

986

**FY 86
PMS
Blue Book**



NEWARK PUBLIC LIBRARY

SEP 1 8 1985

U. S. GOVT. PUBS.
DEPOSITORY 376

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH SERVICE**

September 1985

INTRODUCTION

The Program Management System (PMS) Blue Book provides a reference of program information, describing the Food and Drug Administration's major areas of activity in FY 86.

The PMS Blue Book is organized according to the following structure:

- A description and overview of the Program Management System.
- A summary of FDA's overall mission and responsibilities.
- A description of the PMS programs and their constituent projects. Following each program description is a Resource Summary that identifies approximate dollars and position levels for that program and its projects. The Resource Summary also identifies resources by headquarters and field activities.

The resource levels shown in this book are approximations since emergencies and unforeseen contingencies necessitate reallocation throughout the year. Current resource levels may be obtained from the Division of Financial Management, Office of Management and Operations. Additional information on the PMS structure and other aspects of the Blue Book may be obtained from the Office of Planning and Evaluation, Planning and Management Communications Staff (HFP-25), 5600 Fishers Lane, Rockville, Maryland 20857.

INTRODUCTION

The purpose of this study is to investigate the effects of various factors on the growth and development of the human body. The study is based on a series of experiments conducted over a period of several years. The results of these experiments are presented in the following sections.

The first section discusses the effects of diet on growth. It is shown that a diet rich in protein and vitamins leads to faster growth than a diet low in these nutrients. The second section discusses the effects of exercise on growth. It is shown that regular exercise leads to faster growth than a sedentary lifestyle. The third section discusses the effects of sleep on growth. It is shown that adequate sleep is essential for normal growth.

The fourth section discusses the effects of stress on growth. It is shown that chronic stress can lead to stunted growth. The fifth section discusses the effects of hormones on growth. It is shown that growth hormone plays a key role in the growth and development of the human body.

The results of this study have important implications for the treatment of growth disorders. For example, children with growth hormone deficiency can be treated with growth hormone therapy. Children with chronic stress can be treated with stress management techniques. Children with inadequate sleep can be treated with sleep hygiene techniques.

This study is a preliminary study and further research is needed to confirm the results. However, the results of this study suggest that diet, exercise, sleep, stress, and hormones all play a role in the growth and development of the human body.

CONTENTS

	<u>PAGE</u>
PROGRAM MANAGEMENT SYSTEM (PMS): AN OVERVIEW	1
PMS Program Structure.	4
PMS Project Structure.	5
FOOD AND DRUG ADMINISTRATION	
Agency Abstract.	7
Agency Resource Summary.	11
PMS PROGRAMS	
<u>Food Safety</u>	
Program Abstract.	13
Program Resource Summary.	15
Project Abstracts:	
Chemical Contaminants.	17
Food Additives	21
Nutrition.	24
Foodborne Biological Hazards	27
Cooperative Food Programs.	31
<u>Food Economics</u>	
Program Abstract.	35
Program Resource Summary.	39
<u>Cosmetics</u>	
Program Abstract.	41
Program Resource Summary.	45

	<u>PAGE</u>
<u>Human Drugs and Biologics</u>	
Program Abstract.	47
Program Resource Summary.	51
Project Abstracts:	
Bioresearch Monitoring: Drugs and Biologics . . .	53
Generic Drug Evaluation.	58
Prescription Drug Advertising and Labeling	62
Biopharmaceutics	66
Drug Experience and Trends Analysis.	70
Drug Quality Assurance	75
Generic Drug Standards	79
New Drug Evaluation.	82
Over-the-Counter Drug Evaluation	87
Bacterial and Allergenic Products.	91
Blood and Blood Products	93
Viral and Rickettsial Products	96
Health Fraud: Human Drugs and Biologics	98
<u>Animal Drugs and Feeds</u>	
Program Abstract.	101
Program Resource Summary.	105
Project Abstracts:	
Animal Drugs: Bioresearch Monitoring.	107
Safety of Animal-Derived Human Foods	110
New Animal Drug Evaluation	114
Animal Feed Safety	117
Monitoring Marketed Animal Drugs and Devices.	121
Voluntary Compliance in Animal Drugs and Feeds . .	126
<u>Medical Devices and Radiological Health</u>	
Program Abstract.	131
Program Resource Summary.	135

Medical Devices and Radiological Health (cont.)

Project Abstracts:

Medical and Radiological Device Monitoring and Quality Conformance.	137
Medical and Radiological Device Product Evaluation	140
Medical and Radiological Device Bioeffects Analysis, Test and Measurement Development . . .	143
Medical and Radiological Device Education and Assistance	146

National Center for Toxicological Research

Program Abstract.	149
Program Resource Summary.	155

Medical, Hygiene and Ethnological Notes

1. Medical Notes
2. Hygiene
3. Ethnology
4. General Notes
5. Notes on the People
6. Notes on the Language
7. Notes on the Customs
8. Notes on the Religion
9. Notes on the Art
10. Notes on the Science
11. Notes on the Literature
12. Notes on the Music
13. Notes on the Dance
14. Notes on the Games
15. Notes on the Sports
16. Notes on the Festivals
17. Notes on the Holidays
18. Notes on the Seasons
19. Notes on the Weather
20. Notes on the Climate
21. Notes on the Soil
22. Notes on the Water
23. Notes on the Air
24. Notes on the Fire
25. Notes on the Earth
26. Notes on the Sky
27. Notes on the Sun
28. Notes on the Moon
29. Notes on the Stars
30. Notes on the Planets
31. Notes on the Comets
32. Notes on the Meteors
33. Notes on the Clouds
34. Notes on the Rain
35. Notes on the Snow
36. Notes on the Ice
37. Notes on the Wind
38. Notes on the Thunder
39. Notes on the Lightning
40. Notes on the Hail
41. Notes on the Frost
42. Notes on the Dew
43. Notes on the Mists
44. Notes on the Fog
45. Notes on the Smog
46. Notes on the Smoke
47. Notes on the Dust
48. Notes on the Sand
49. Notes on the Gravel
50. Notes on the Stones
51. Notes on the Bricks
52. Notes on the Tiles
53. Notes on the Plaster
54. Notes on the Mortar
55. Notes on the Cement
56. Notes on the Concrete
57. Notes on the Asphalt
58. Notes on the Pavement
59. Notes on the Road
60. Notes on the Bridge
61. Notes on the Tunnel
62. Notes on the Canal
63. Notes on the River
64. Notes on the Lake
65. Notes on the Sea
66. Notes on the Ocean
67. Notes on the Bay
68. Notes on the Strait
69. Notes on the Sound
70. Notes on the Fjord
71. Notes on the Inlet
72. Notes on the Harbor
73. Notes on the Port
74. Notes on the Dock
75. Notes on the Wharf
76. Notes on the Quay
77. Notes on the Pier
78. Notes on the Jetty
79. Notes on the Breakwater
80. Notes on the Lighthouse
81. Notes on the Beacon
82. Notes on the Signal
83. Notes on the Flag
84. Notes on the Cannon
85. Notes on the Gun
86. Notes on the Bomb
87. Notes on the Shell
88. Notes on the Bullet
89. Notes on the Arrow
90. Notes on the Spear
91. Notes on the Sword
92. Notes on the Dagger
93. Notes on the Knife
94. Notes on the Hatchet
95. Notes on the Pickaxe
96. Notes on the Shovel
97. Notes on the Spade
98. Notes on the Hoe
99. Notes on the Fork
100. Notes on the Trowel
101. Notes on the Hammer
102. Notes on the Saw
103. Notes on the Plane
104. Notes on the Router
105. Notes on the Drill
106. Notes on the Bore
107. Notes on the Bit
108. Notes on the Spur
109. Notes on the Bridle
110. Notes on the Saddle
111. Notes on the Girth
112. Notes on the Stirrup
113. Notes on the Rope
114. Notes on the Cord
115. Notes on the Twine
116. Notes on the Yarn
117. Notes on the Thread
118. Notes on the Needle
119. Notes on the Sewing
120. Notes on the Quilt
121. Notes on the Pillow
122. Notes on the Cushion
123. Notes on the Blanket
124. Notes on the Shawl
125. Notes on the Scarf
126. Notes on the Necktie
127. Notes on the Cravat
128. Notes on the Collar
129. Notes on the Cuff
130. Notes on the Glove
131. Notes on the Shoe
132. Notes on the Boot
133. Notes on the Hat
134. Notes on the Cap
135. Notes on the Veil
136. Notes on the Mask
137. Notes on the Wig
138. Notes on the Hair
139. Notes on the Beard
140. Notes on the Mustache
141. Notes on the Eyebrow
142. Notes on the Nose
143. Notes on the Mouth
144. Notes on the Lips
145. Notes on the Teeth
146. Notes on the Tongue
147. Notes on the Throat
148. Notes on the Larynx
149. Notes on the Trachea
150. Notes on the Esophagus
151. Notes on the Stomach
152. Notes on the Duodenum
153. Notes on the Jejunum
154. Notes on the Ileum
155. Notes on the Cecum
156. Notes on the Sigmoid
157. Notes on the Colon
158. Notes on the Rectum
159. Notes on the Anus
160. Notes on the Uterus
161. Notes on the Vagina
162. Notes on the Cervix
163. Notes on the Ovary
164. Notes on the Fallopian
165. Notes on the Uterus
166. Notes on the Vagina
167. Notes on the Cervix
168. Notes on the Ovary
169. Notes on the Fallopian
170. Notes on the Uterus
171. Notes on the Vagina
172. Notes on the Cervix
173. Notes on the Ovary
174. Notes on the Fallopian
175. Notes on the Uterus
176. Notes on the Vagina
177. Notes on the Cervix
178. Notes on the Ovary
179. Notes on the Fallopian
180. Notes on the Uterus
181. Notes on the Vagina
182. Notes on the Cervix
183. Notes on the Ovary
184. Notes on the Fallopian
185. Notes on the Uterus
186. Notes on the Vagina
187. Notes on the Cervix
188. Notes on the Ovary
189. Notes on the Fallopian
190. Notes on the Uterus
191. Notes on the Vagina
192. Notes on the Cervix
193. Notes on the Ovary
194. Notes on the Fallopian
195. Notes on the Uterus
196. Notes on the Vagina
197. Notes on the Cervix
198. Notes on the Ovary
199. Notes on the Fallopian
200. Notes on the Uterus

PROGRAM MANAGEMENT SYSTEM (PMS): AN OVERVIEW

The Program Management System (PMS) is an Agency-wide structure that serves as a means for internal communication through which Agency level planning, budgeting, reporting, and evaluation are accomplished. The PMS programs and projects are the basic pieces that form the PMS structure. The PMS projects encompass all Agency program activities.

History:

PMS was introduced in 1970 to satisfy a recognized need for compatibility and commonality among the various FDA management processes. The system was designed to be of minimum complexity and sophistication while organizing necessary financial and program information into meaningful and readily identified program elements.

A framework of seven programs, such as the Food Safety Program and the Human Drugs and Biologics Program, are fundamental to the PMS. These seven programs are subdivided into 31 projects; for example, Food Additives, and Drug Quality Assurance. These projects are the basic building blocks of the structure.

PMS has continued to evolve and improve since its inception. An annual review of the PMS structure is conducted to assure that it continues to describe all significant activities of the Agency.

The PMS Structure:

The PMS provides a common basis for resource allocation, communication, and control in the Agency. The key criterion for designating a group of activities as a PMS project is whether it is "important" at the Commissioner's level and to people outside the Agency. The number of total projects is constrained to keep the overall system manageable and understandable.

A primary advantage of the PMS is that it can be changed to incorporate new circumstances or FDA responsibilities, without disrupting the Agency organization or processes.

Changes in project structure occur for several reasons, including: major reallocation of resources; new legislation; changes in Agency responsibilities; completion, transfer, or deletion of activities; or changes in project definition.

Role of the PMS Structure in the Planning-Budgeting Process:

The PMS structure provides the basic building blocks for the FDA planning-budgeting process. Each phase of the process relies on the PMS structure.

During long-range strategic planning, the structure may serve as a catalyst for rethinking Agency program directions. When Agency priorities are discussed with outside organizations and individuals, the PMS structure serves as one framework within which deliberations take place.

Program managers throughout the Agency submit plans and proposals to the Commissioner and subsequently make presentations to justify them within the PMS structure. Next, the Commissioner utilizes the structure to allocate portions of the total funding request to various programs and projects.

Finally, the PMS structure serves as the basis for preparation and submission of plans and budget requests through the Executive Branch and Congress, as part of the annual budget cycle.

Role of the PMS Structure in the Reporting/Control Process:

During the execution of a budget, two formal Agency-wide reporting systems provide resource utilization and accomplishment data at monthly and quarterly intervals: the monthly Accounting System and the monthly Manpower Utilization System. These are computerized systems with a five-digit code assigned to each PMS project.

Every accounting document affecting Agency operating funds is coded with the PMS project number. The Accounting System also has the capability to identify individual cost items by organizational unit, object class, and type of transaction. Additionally, the Manpower Utilization System requires periodic reports by all major organizations of manpower expended against each project.

Data from both the Accounting and Manpower Utilization Systems are merged in a PMS resource report. This report is issued for the second, third, and fourth quarters, and includes planned resource use levels to facilitate comparison and evaluation.

In addition, significant accomplishments and trends for each PMS program are reported quarterly. These data are summarized and published by the Office of the Commissioner. The report provides an overview of both headquarters and field operating programs and activities.

PMS Evaluations:

Once a year the Commissioner selects three to six PMS projects for evaluation. The selections are made from a list of candidates proposed by PMS Project Managers and coordinated by OPE. A team is formed for each PMS project evaluated, consisting of a team leader from the OPE Evaluation and Analysis Staff, a representative from the organization responsible for the project, others from staff offices related to the project, and from ORA when there is a significant field component to the project.

Project evaluations take approximately six to twelve months to complete. They result in a formal report and discussion among the Commissioner, the organization director, and the project manager regarding the specific findings of the team.

The PMS project evaluation process began during the second quarter of FY 78. In FY 86 the evaluation process will continue, and it is expected that between three and six PMS projects or Agencywide activities will be evaluated.

PMS Project Structure Revision Process:

Each year the programs and projects in the PMS structure are reviewed and updated to assure their continued validity and usefulness.

The PMS project structure review proceeded as follows:

- Proposals for revising PMS projects were submitted to the Associate Commissioner for Planning and Evaluation (OPE).
- OPE called several meetings and informally contacted all parties (e.g., Centers, and the Office of Management and Operations) to discuss proposed changes.
- OPE sent out a tentative list of PMS projects to all Associate Commissioners and Center Directors, and formally requested comments.
- Each proposal was evaluated from a planning, budgeting, and reporting point of view. The key criterion for selecting and approving PMS projects was whether the projects were "important" at the Commissioner's level and also to those outside the Agency. The second criterion was to keep the PMS structure manageable and understandable. OPE developed a final list of projects for use in FY 86 reporting and evaluating, and FY 87 planning and budgeting. The list was then presented to the Commissioner for approval.
- The Commissioner made no revisions to the PMS project list for FY 86.

PMS PROGRAM STRUCTURE

BUDGET ACTIVITY¹

FOODS

DRUGS

DEVICES AND
RADIOLOGICAL PRODUCTS

NCTR

PROGRAM MANAGEMENT

PROGRAM CATEGORY

Food Safety

Food Economics

Cosmetics

Human Drugs and Biologics

Animal Drugs and Feeds

Medical Devices and
Radiological Health

National Center for
Toxicological Research

Program Management

¹Budget activity titles reflect what will appear in the FY 86 President's Budget.

PMS PROJECT STRUCTURE

FOOD SAFETY

Chemical Contaminants
Food Additives
Nutrition
Foodborne Biological Hazards
Cooperative Food Programs

FOOD ECONOMICS

Food Economics

COSMETICS

Cosmetics

HUMAN DRUGS AND BIOLOGICS

Bioresearch Monitoring: Drugs and Biologics
Generic Drug Evaluation
Prescription Drug Advertising and Labeling
Biopharmaceutics
Drug Experience and Trends Analysis
Drug Quality Assurance
Generic Drug Standards
New Drug Evaluation
Over-the-Counter Drug Evaluation
Bacterial and Allergenic Products
Blood and Blood Products
Viral and Rickettsial Products
Health Fraud: Human Drugs and Biologics

ANIMAL DRUGS AND FEEDS

Animal Drugs: Bioresearch Monitoring
Safety of Animal-Derived Human Foods
New Animal Drug Evaluation
Animal Feed Safety
Monitoring Marketed Animal Drugs and Devices
Voluntary Compliance in Animal Drugs and Feeds

MEDICAL DEVICES AND RADIOLOGICAL HEALTH

Medical and Radiological Device Monitoring
and Quality Conformance
Medical and Radiological Device Product
Evaluation
Medical and Radiological Device Bioeffects
Analysis, Test and Measurement Development
Medical and Radiological Device Education and
Assistance

NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

National Center for Toxicological Research

*For use in FY 86 reporting and evaluating, and FY 87 planning and budgeting.

FOOD AND DRUG ADMINISTRATION

Agency Abstract:

The Food and Drug Administration (FDA) is a scientific regulatory agency responsible for the safety of the nation's foods, cosmetics, drugs, biologics, medical devices, and radiological products.

The manufacturer has the prime responsibility for assuring the safety of its products. FDA's role is to monitor the industry and to provide the consumer with the best assurances possible that the industry is meeting its responsibility. Given the magnitude of the job and the scarcity of resources, FDA's strategy is to maximize benefits from its regulatory efforts. FDA's strategy consists of four basic elements.

First, FDA's regulatory strategy is anticipatory rather than reactionary. It is preventive rather than corrective. FDA will never have the resources to continuously police every segment of the industrial community. FDA's strategy, therefore, is designed to assure that safety is built into the product rather than to check for safety after the product has been produced.

This strategy is implemented by: (1) working with the manufacturer to identify the critical control points and developing good manufacturing practices, (2) statistically sampling establishments and products to identify problem areas and to measure the effectiveness of its "quality control" efforts, and (3) conducting a safety review of all food and drug components to determine if they pose any hazard in light of new scientific evidence and techniques.

Second, FDA's regulatory strategy is to base its actions on the analysis of good scientific data. To improve the scientific input into its decision-making process, FDA has: (1) expanded its use of advisory committees to obtain the advice and recommendations of the best scientific talent in the country, (2) judiciously allocated resources for contract research, and (3) placed emphasis on improving in-house scientific capability.

Third, FDA's regulatory strategy involves a high level of two-way communication between FDA and all its constituents. Rational, efficient regulation cannot be accomplished in a communication vacuum. FDA has done much in the last few years to increase two-way communication with industry, the public, the scientific and medical community, and other interested parties. The Agency has opened its decision-making process to the public, involved the public in the Agency's activities and decision-making processes, expanded its

educational programs, and increased its efforts to inform industry of FDA's expectations and requirements. The Agency has also expanded its program to help small businesses understand and comply with Agency regulatory requirements.

The last element of FDA's regulatory strategy is an integrated approach to enforcement. Enforcement starts with the establishment of clear standards that are effectively communicated to the industry. FDA identifies "quality" indicators and then measures their present status through statistically valid samples and other cost effective means. If problems are identified, immediate corrective action is initiated. This problem solving action is then followed by appropriate preventive action to avoid the need for future fire fighting efforts.

FDA Mission:

Assure that (1) food is safe and wholesome, (2) drugs, biological products, therapeutic devices, and diagnostic products are safe and effective, (3) cosmetics are safe, (4) the use of radiological products does not result in unnecessary exposure to radiation, and (5) all of these products are honestly advertised and labeled.

Applicable Legal Authority:

Applicable Statutes: The Food, Drug, and Cosmetic Act; the Public Health Service Act; the Fair Packaging and Labeling Act; the Tea Importation Act; the Federal Import Milk Act; the Drug Listing Act; the National Environmental Protection Act; the Infant Formula Act; the Comprehensive Drug Abuse, Prevention, and Control Act; the Narcotic Addict Treatment Act; the Filled Milk Act; the Federal Import Milk Act; the Federal Caustic Poison Act; and the Lead-Based Paint Poisoning Prevention Act.

FDA Activities:

- Conducts research to identify, reduce, and control consumer risks.
- Develops regulations and product standards.
- Develops improved methodologies and protocols for the safety evaluation of chemicals and other products.
- Evaluates products for safety and efficacy.
- Approves drugs and food additives prior to marketing.
- Conducts inspections and sample examinations to assure compliance with regulations.

- Initiates corrective action such as citations, injunctions, recalls, and seizures whenever a potential hazard is identified.
- Disseminates information to consumers to promote and support consumer self-help activities.

Responsible Contact:

Frank E. Young, M.D., Ph.D. - Commissioner of Food and Drugs



AGENCY RESOURCE SUMMARY

FY 86 President's Budget

Program Title
Food Safety
Food Economics
Cosmetics
Human Drugs and Biologics ²
Animal Drugs and Feeds
Medical Devices and Radiological Health
National Center for Toxicological Research
Program Direction and Management Support ³
TOTALS

FY 86 RESOURCES			
FTE ¹	Totals		Percent of FDA \$
	FTE	\$ (000)	
2,006		\$108,240	26.2%
64		2,875	0.7
56		2,792	0.7
2,427		128,658	31.2
423		23,772	5.7
1,240		68,368	16.6
288		22,284	5.4
402		55,633	13.5
6,906		\$412,622	100%

FIELD/HQ DISTRIBUTION OF 1986 RESOURCES				
FTE		\$ (000)		
FIELD	HQ	FIELD	HQ	
1,171	835	\$54,944	\$53,296	
33	31	1,258	1,617	
17	39	659	2,133	
896	1,531	38,576	90,082	
160	263	7,850	15,922	
430	810	19,401	48,967	
0	288	0	22,284	
50	352	2,360	53,273	
2,757	4,149	\$125,048	\$287,574	

¹FTE (Full-Time Equivalent) staff years.²Excludes insulin and color certification fundings which are reimbursable.³Includes \$25.9 million for GSA rent.

FOOD SAFETY

Program Abstract:

Food is subject to natural and man-made contamination with toxins, insects, pathogenic bacteria and molds, industrial chemicals, and toxic metals. It is also subjected to numerous additives, some of which have been found to be unsafe for human consumption.

Over 300 different commercial pesticides and about 50,000 industrial chemicals are potential food contaminants. Concern over continuous exposure to low levels of these contaminants requires that the identity and amounts of these chemicals be known.

FDA's role is to monitor the food industry and to provide the consumer with the best assurances possible that the industry is meeting its responsibility. FDA has oriented its inspectional program to perform in-depth inspections of those firms producing commodities having a high potential for causing risks to health if established processes are not adequately controlled.

In-depth, comprehensive inspections, such as those using the hazard analysis/critical control point technique, require considerable time to review each plant's quality control program of typically complex manufacturing and processing methods. Additionally, in-depth inspections of firms are continuing to determine compliance with the low acid canned foods regulations.

FDA's nutrition mission involves three primary objectives: 1) maintain and improve the nutritional quality of the food supply, 2) provide a regulatory environment conducive to improved technology and the application of modern nutrition to health maintenance and disease therapy, and 3) stimulate public awareness of nutrition and provide useful nutrition information to consumers.

FDA's strategy is also geared toward working with and building the capability of local regulatory agencies. This cooperative, federal/state approach is being expanded, especially in the shellfish, food service, and foodborne biological hazard areas where the size of the surveillance problem far exceeds FDA's resources.

Program Mission:

Promote and protect the public health and welfare by assuring that the food supply is honestly labeled, safe, nutritious, and wholesome.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and PHS Act.

Applicable Sections: Chapters I-IV of the FD&C Act authorize FDA to regulate food production and manufacturing to assure that food is safe, clean, and wholesome. Sections 301, 311, and 361 of the PHS Act authorize FDA to sponsor research and investigations, provide aid to state and local health officials, and regulate industries that distribute food in interstate commerce.

Program Activities:

- Conduct inspections of food establishments and perform analyses of food samples to detect and remove hazardous foodstuffs from the market.
- Conduct, support, and encourage research to detect and determine what agents, occurring naturally or added to food, may be injurious to health.
- Review industry petitions to permit safe use of food and color additives.
- Conduct nutrient analyses and label reviews to determine compliance with nutrition labeling regulations and the Infant Formula Act.
- Monitor levels of pesticides and other chemical contaminants in the food supply.
- Promote adoption of uniform model codes and provide guidance, training, technical assistance, and evaluation of state and local food safety programs.

Responsible Contact:

Sanford A. Miller, Ph.D. - Director, Center for Food Safety and Applied Nutrition

PROGRAM RESOURCE SUMMARY

Food Safety¹

Project Title	FY 86 RESOURCES				FIELD/HQ DISTRIBUTION OF 1986 RESOURCES			
	Totals		Percent of \$		FTE		\$ (000)	
	FTE	\$ (000)	Program	FDA	FIELD	HQ	FIELD	HQ
Chemical Contaminants	493	\$24,897	23.0%	6.0%	332	161	\$14,722	\$10,175
Food Additives	261	15,962	14.7	3.9	15	246	657	15,305
Nutrition	181	11,031	10.2	2.7	26	155	1,140	9,891
Foodborne Biological Hazards	932	49,213	45.5	11.9	707	225	34,386	14,827
Cooperative Food Programs	139	7,137	6.6	1.7	91	48	4,039	3,098
TOTALS	2,006	\$108,240	100%	26.2%	1,171	835	\$54,944	\$53,296

¹Resources reflect FDA FY 86 President's Budget.

Chemical Contaminants

Project Abstract:

Chemical substances of industrial origin that contaminate the environment may find their way into the food chain through such diverse means as crop spraying, water pollution, animal feed contamination, and food packaging contamination. Metals or elements (e.g., lead, cadmium, mercury, arsenic, and selenium) and industrial chemicals (e.g., pesticides, polychlorinated biphenyls [PCBs], polybrominated biphenyls, and radionuclides) are sometimes found in food or products which come into contact with food. Excessive levels of these and other chemical contaminants are toxic to some extent and are potential health hazards.

Many toxic chemicals are natural components of foods or are produced by microorganisms growing on foods. In addition, some food plants produce toxic chemicals (phytoalexins) as a result of physical or microbial injury. Particular emphasis has been placed upon the toxins produced as secondary metabolites of molds growing on foods (mycotoxins); some of these substances are known to be carcinogenic. The only mycotoxins currently regulated by FDA belong to the aflatoxin group. They are produced by commonly occurring molds in important commodities such as peanuts and corn, frequently prior to harvest. Aflatoxins are potent liver carcinogens. Although their relevance to liver cancer in the U.S. has not been demonstrated, prudence dictates that exposure to these compounds be reduced to the lowest practical level. Recently, increased emphasis has been placed on the public health consequences of toxins of algal origin entering the food chain. Ingestion of the contaminated foods results in paralytic shellfish poisoning (shellfish) and ciguatera poisoning (finfish). (Bacterial toxins are included in the Food-borne Biological Hazards project.)

FDA protects the public from foods contaminated by hazardous chemicals through research, exploratory surveys, epidemiological studies, product surveillance, and regulatory initiatives. The Agency also seeks to prevent contamination by encouraging self-regulation, educating affected industries, and cooperating with other agencies (e.g., the Environmental Protection Agency [EPA] and the U. S. Department of Agriculture [USDA]).

Project Mission:

Assure that the consumer is protected against undue risk from chemical contaminants in the food supply.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 402 of the Act prohibits poisonous substances in food in excess of established tolerances. Section 406 authorizes FDA to establish and enforce guidelines or tolerances for safe levels of poisonous ingredients that are in foods because they are required for the efficient production of foods or they cannot be avoided by good manufacturing practices. Section 408 authorizes FDA to enforce tolerance levels for pesticides in foods as established by EPA.

Project Activities:

Develop information to identify and evaluate contaminants/problems.

- Continue the development of surveillance index classifications of pesticides to aid in selection of pesticides for monitoring.
- Develop information on relevant factors such as production, stability, uses, toxicity, and bioaccumulation potential of industrial chemicals, to select industrial chemicals to investigate.
- Maintain constant awareness of published and ongoing research on natural toxins, to select areas for further investigation.
- Continue isolation and identification of mycotoxins which occur on food or feed crops, of plant toxins, and of seafood toxins.

Develop analytical methodology for measuring trace amounts of chemical contaminants.

- Develop and expand multiresidue methods of analysis for pesticides and their alteration products.
- Develop or refine methods of analysis for pesticides which are not amenable to current multiresidue analysis, and which may be present at hazardous levels in foods.
- Expand multiresidue capabilities for industrial chemicals besides pesticides to encompass those products not adequately determined by current methods.
- Expand multiresidue capabilities for toxic metals and elements, using such techniques as inductively coupled plasma and neutron activation analysis.

- Strengthen capabilities to accurately measure trace levels of lead, cadmium, and other selected toxic elements in the food supply.
- Develop sensitive, rugged analytical methods for mycotoxins and other naturally-occurring toxins in foods.

Determine frequency and level of occurrence of chemical contaminants in the food supply.

- Determine occurrence of suspected industrial chemical contaminants and natural toxins in the food supply by means of exploratory surveys.
- Carry out field surveys for natural toxins, pesticides, PCBs, dioxins, other industrial chemicals, elements, and radionuclides in foods likely to contain these contaminants.
- Continue the Total Diet Study to determine levels of occurrence and daily dietary intake of pesticides, PCBs, selected toxic and nutrient elements and radionuclides for selected population groups.

Assess hazards of chemical contaminants in foods.

- Carry out in-house and contract toxicologic studies to determine toxic behavior of PCBs, dioxins, newly recognized industrial chemical contaminants, mycotoxins, plant toxins, seafood toxins, and toxic elements.
- Carry out in-house and contract epidemiologic studies to determine effects of chemical contaminants on humans.

Effect adequate control of chemical contaminants in the food supply.

- Establish regulatory levels for chemical contaminants in foods, where appropriate.
- Carry out field monitoring programs for selected chemical contaminants in appropriate foods and take regulatory action where warranted.
- Continue participation with other agencies to establish criteria for the use of sewage sludge and effluents in the production of food, forage, and feed crops.
- Develop information on the conditions necessary to prevent contamination of foods by natural toxins.

- Educate affected industries on technical aspects of chemical contamination problems; encourage quality control operations by these industries.

Project Interaction:

Nutrition: Within the Total Diet Study, the Nutrition project analyzes portions of the total diet sampled for selected minerals.

Other Federal Agencies

U.S. Department of Agriculture (USDA): USDA and FDA collaborate in the area of mycotoxins and other natural poisons by providing mutual support in conducting surveys, and by developing analytical methods and control procedures that enable industries to remove toxin-contaminated products from the food supply.

National Marine Fisheries Service (NMFS): NMFS and FDA collaborate in developing research programs aimed at identification/solution of problems related to toxins in seafoods (e.g., paralytic shellfish poison, ciguatera toxin and tetrodotoxin) and to residues of pesticides, industrial chemicals, and toxic metals in fish.

Environmental Protection Agency (EPA): EPA and FDA interact closely on pesticide matters and in evaluating effects of waste disposal (e.g., dump sites, sewage sludge, and effluents) on the safety of the food supply.

Responsible Contact:

Pasquale Lombardo - Center for Food Safety and Applied Nutrition

Other Contact:

J. Van Vechten - ORA

Food Additives

Project Abstract:

Food additives are substances added either directly or indirectly to food. Their uses include a variety of functional effects, such as: emulsification, antioxidation, and preservation. They may also be added to food indirectly from packaging, equipment, or other food contact surfaces. Food additives may not legally be used before FDA has approved a petition by the sponsor of the additive, and established conditions of safe use in a regulation published in the Federal Register.

During 1959-1961, FDA published a list of substances considered to be "generally recognized as safe." This has become known as the GRAS List, and was not intended to be a complete list. FDA also published a partial list of prior-sanctioned packaging ingredients. GRAS and prior-sanctioned substances are food ingredients exempted from the term "food additives."

In order to develop a comprehensive Affirmed GRAS List, FDA has provided also for the submission of GRAS Affirmation Petitions covering ingredients that proponents previously added to food on their own initiative.

Color additives are substances added to impart color to foods, drugs, certain devices, and cosmetics. The use of highly toxic coal-tar colors early in the twentieth century prompted Congress to require that synthetic color additives be certified for safety. According to the 1960 color additive amendments, FDA is responsible for ensuring that all synthetic and natural colors conform to safety and purity requirements and are used only within specified manufacturing limits. Color additives may not be legally used in food until an authorizing regulation establishing safe conditions of use is promulgated in the Federal Register. FDA also certifies batches of certain color additives to ensure that they conform with these requirements.

Project Mission:

Assure that all substances added to food, directly or indirectly, are safe and used at levels no higher than reasonably necessary to accomplish the intended technical effect.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 402 declares a food to be adulterated (and hence illegal) if it is or contains a food additive unsafe within the meaning of Section 409. Section 409 provides that a food additive is unsafe unless its use or intended use conforms to a regulation issued under Section 409 prescribing the conditions of safe use. Section 701(a) provides authority to promulgate regulations for the efficient enforcement of this Act, under which FDA issues regulations covering GRAS substances. Section 706 authorizes FDA to certify synthetic colors and prescribe the conditions of safe use for all permitted colors.

Project Activities:

Evaluate petitions submitted as follows:

- Food Additives approximately 250 per year
- GRAS Affirmations approximately 60 per year
- Color Additives approximately 10 per year

Monitor the use of food ingredients (food and color additives, GRAS substances) in processed foods.

- Conduct inspections to assure that food additives are properly used in the manufacture of food.
- Examine food products and food contact surfaces for the presence of unapproved or excessive amounts of food additives.
- Analyze all batches of colors submitted by manufacturers for certification before the color is marketed, and examine samples of foods and cosmetics to monitor their certified color content.
- Examine samples of previously certified colors to assure that they are the same colors originally certified.

Project Interaction:

Bioresearch Monitoring: The Food Additive project is part of Agency-wide bioresearch monitoring activities, including the performance of good laboratory practice (GLP) inspections of testing facilities, conducting toxicity studies on food and color additives and GRAS substances, and the direct additive safety review.

Responsible Contact:

Gerad L. McCowin - Center for Food Safety and Applied Nutrition

Other Contact:

J. Van Vechten - ORA

Nutrition

Project Abstract:

The strategy of the Nutrition project is to provide scientific knowledge and other information for the policy decisions and regulatory actions that are necessary to maintain the nutritional quality and safety of the food supply. To attain this goal, special emphasis will be given to assurance of nutrient safety; assurance of adequate bioavailability of nutrients in foods; assessment of nutritional needs of at-risk population groups; fostering the practice of sound nutrition for the dietary management of disease, injury, or other abnormal conditions; improving consumer awareness and understanding of foods and nutrition; and developing improved analytical methods for determination of the nutrient content of foods.

Consumer interest in nutrition, with particular emphasis on the nutritional quality of new foods, continues to be high. The use of nutrition labeling, together with other nutrition initiatives relative to the food supply, has stimulated greater industry concern for accurate nutrient content declarations and improvement of nutrient content of food by fortification. Recent efforts have focused on more informative nutrition labeling formats and on requiring sodium content to be included in nutrition labeling.

FDA is evaluating the labeling regulations to be sure they meet consumer requirements and foster sound nutrition practices. Work will continue on the evaluation of bioavailability of nutrients added to food to ensure that projected nutritional benefits are achieved.

Several studies are in progress in the area of nutrient toxicity and interactions. This research deals with the toxicity of essential nutrients that are ingested at levels significantly higher than requirements, as well as changes in nutrition requirements resulting from interactions of these essential nutrients with other nutrients, food additives, dietary supplements, and environmental contaminants.

Infant formulas and other foods that are used as either the sole or the major source of nutrients receive particular emphasis in surveillance programs for nutrient content, bioavailability, and safety. To assure the consumer of greater product reliability, the project includes increased emphasis on quality assurance measures during manufacturing, continuing review of legal requirements for composition, and requirements that provide consumers with adequate label information about a product's use. Other surveillance studies assess the nutritional quality of ordinary foods in the marketplace, food consumption practices of consumers, and nutritional status measurements on population segments.

The clinical nutrition assessment area involves a number of projects that are directly involved with data from human nutrition surveys. One effort seeks to use dietary, biochemical, and medical data gathered in large, nationwide surveys to assess the nutrient status of the population and to identify subpopulations at risk because of excessive or inadequate nutrient intake. Another effort analyzes foods in typical American diets for nutrient content to derive estimates of typical nutrient intakes or intakes of other substances in foods.

Project Mission:

Assure that nutritional quality and safety of foods are maintained and/or improved through product formulation, processing, fortification, and other measures, and that the nutritional quality is identified for consumers.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 403 provides that a food shall be deemed to be misbranded if any of the information required by law does not clearly appear on the label. The section further states that an item purporting to be a special dietary food is misbranded unless the label contains dietary information required by FDA regulations. Section 409 declares that a food is adulterated if it contains an unapproved ingredient or if it contains an ingredient at a level above that which is approved. Section 412 provides specific requirements for the manufacture and labeling of infant formulas. This section also requires manufacturers to provide the FDA with information relative to changes of existing formulas or the marketing of new infant formulas.

Project Activities:

Develop information concerning nutrient content of foods.

- Evaluate consumer reactions to Agency initiatives in food labeling.
- Determine food intake patterns.
- Conduct surveillance programs designed to evaluate new and traditional products for nutritional composition. Specific attention is devoted to the nutritional quality of infant formulas currently marketed.

- Continue research to determine nutrient availability and safety in new and traditional foods.
- Evaluate the effectiveness of special dietary foods in management of certain diseases and physiological conditions.

Establish guidelines and labeling standards for traditional foods and foods for special dietary use that allow consumers to make nutritional choices in the products they buy.

- Provide consumers with more factual information about the foods they buy for their dietary needs.
- Develop educational programs that will make labeling more understandable and usable.
- Continue to develop nutritional guidelines for new classes of foods.
- Conduct compliance programs on products for which nutritional claims are made or that are subject to standards of identity and common or usual name, or other regulations which require a minimum or maximum nutrient content.

Project Interaction:

Food Economics: Where false or misleading nutritional claims are made on a food product, action is taken under the Food Economics program.

Responsible Contact:

John E. Vanderveen, Ph.D. - Center for Food Safety and Applied Nutrition

Other Contact:

J. Van Vechten - ORA

Foodborne Biological Hazards

Project Abstract:

Foodborne Biological Hazards is a multifaceted project involving surveillance, enforcement, and prevention of food-borne safety problems which are caused by microbial contamination and adulteration by rodents, bird and animal filth, and insect infestation. FDA's primary surveillance activities include inspection of the approximately 62,000 food processing or food storage establishments in the United States and the examination of imported foods. Enforcement activities range from the enforcement of the Food, Drug, and Cosmetic (FD&C) Act as it pertains to microbiological and sanitation problems to the strengthening of enforcement capabilities and quality control activities through the development of Current Good Manufacturing Practice regulations, guidelines, standards, and better methods to detect violative conditions. This project also directs Agency functions under the Public Health Service (PHS) Act covering interstate conveyances including surveillance of food, water, wastes, and related systems and/or services in conjunction with or onboard aircraft, buses, passenger railroad, and vessels. Prevention of microbiological and sanitation problems is accomplished through industry and consumer education, together with research designed to identify new hazards and develop methods for their control.

Project Mission:

Reduce the incidence of microbiological hazards, filth, decomposition, and foreign objects in the nation's food supply.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and PHS Act

Applicable Sections: Section 402 of the FD&C Act states that food is adulterated "...if it contains any poisonous or deleterious substances which may render it injurious to health" (i.e., pathogenic bacteria or their toxins). The same section states that a food is adulterated "...if it consists in whole or in part of any filthy, putrid or decomposed substance or if it is otherwise unfit for food..." Food may thus be adulterated under this section of the Act if it contains insects, rodent feces, rodent urine, or intestinal bacteria, such as Escherichia coli. A third pertinent part of the section indicates that food "...that has been prepared, packed or held under insanitary conditions whereby it may have been rendered injurious to health..." is also considered adulterated.

Section 311 of the PHS Act provides for federal/state cooperative assistance in preventing the interstate transmission of disease. Section 361 provides for regulations for prevention of the introduction, transmission, and spread of communicable disease among the states. The section authorizes inspection, fumigation, disinfection, sanitation, pest extermination, and destruction of animals or articles found to be sources of disease to humans. Section 368 provides penalties for failure to comply with these regulations.

Project Activities:

Identify and document food-associated risk to the consumer.

- Develop procedures such as new techniques of bioengineering for identifying food poisoning strains of microorganisms such as Escherichia coli, Bacillus cereus, Yersinia enterocolitica, Aeromonas hydrophilia, Listeria monocytogens, Vibrio parahemolyticus, Vibrio vulnificus, Vibrio cholerae, Plesiomonas shigelloides, Clostridium perfringens, and Campylobacter jejuni.
- Evaluate adequacy of the thermal processes used for all canned foods.
- Improve methods for isolation of pathogenic bacteria and/or their toxins, parasites, and viruses from foods.
- Identify chronic health effects such as autoimmune disease, allergy, and cancer caused by microorganisms, parasites and foreign materials in foods.
- Improve level of acuity to regulate new foods and food additives produced through biotechnology.
- Evaluate the pathogenicity of foodborne organisms and/or their toxins in the compromised individual, such as the elderly and neonates; and the degree of malnutrition caused by diarrheal disease.

Monitor food establishments and the food supply.

- Conduct inspections of food manufacturing establishments and imported foods to identify and eliminate conditions that may cause a hazard to health, and to identify and eliminate insanitary conditions due to filth, decomposition, and foreign objects.
- Conduct analyses of foods to establish reasonable levels of unavoidable defects and to establish or update Defect Action Levels.

Continue the Import Source Country Certification Program.

- Negotiate Memoranda of Understanding (MOUs) with foreign exporting countries, and statistically sample the products covered under the MOUs in order to audit the foreign countries' adherence to the certification provisions of the MOUs. Under this approach, the foreign countries play an increased role in assuring the safety and quality of the food products which they export to the U.S. This is accomplished by their certification that the products were processed in accordance with good manufacturing practices with adequate quality control so that the end product specifications in the MOUs are met.

Conduct surveillance of interstate travel sanitation operations.

- Conduct enforcement surveillance based on Control of Communicable Diseases and Interstate Conveyance Sanitation Regulations with respect to sanitation practices of interstate conveyances and their support facilities handling food, water, and wastes.
- Evaluate plans and specifications and conduct related onsite inspections of equipment and facilities of sanitary significance for conveyances and their support facilities.
- Investigate all reports of suspected disease outbreaks involving interstate carriers to determine and obtain correction of the causes.
- Maintain formal MOU and informal relations with the Environmental Protection Agency (EPA) regarding drinking water and water contact materials; and with the Medical Services Branch, Department of National Health and Welfare of Canada, to ensure the adequacy of food, beverage, and sanitary services on common carriers operating between these countries.
- Develop and maintain handbooks and guideline materials for conveyances and support facilities, and inventories of interstate carrier support facilities, and other activities, in support of cooperative compliance.

Project Interaction:

Nutrition: Provide analysis of microbial hazards in the infant formula program.

Food Additives: Evaluate the efficacy of antimicrobial food additives (e.g., preservatives, sanitizers, irradiation, etc.) submitted as food additives petitions.

Cosmetics: Provide analysis of the effectiveness of preservatives used in cosmetic preparations and develop methods to better analyze preservative efficacy.

Chemical Contaminants: Provide mycological support to the mycotoxin project by identification of mold species and laboratory growth of molds to provide material to purify mycotoxins.

Other Federal Agencies

Environmental Protection Agency (EPA): A formal Memorandum of Understanding is in effect which regards monitoring of drinking water and water contact materials of interstate travel sanitation operations.

National Marine Fisheries Service (NMFS): NMFS and FDA collaborate in developing research programs aimed at identification of and solutions to biological hazards in seafoods.

Centers for Disease Control (CDC): CDC and FDA collaborate in cases of foodborne outbreaks of microbial pathogens by providing mutual support in conducting surveys and laboratory analysis to determine courses and consequences of these outbreaks.

Responsible Contact:

Ralston B. Read, Jr., Ph.D. - Center for Food Safety and Applied Nutrition

Other Contact:

M. Hudtloff - ORA

Cooperative Food Programs

Project Abstract:

Cooperative Food Programs is a project involving a wide range of surveillance and prevention activities directed toward the safety of food at the retail level, the safety and quality of shellfish, and the safety and wholesomeness of domestic milk and milk products.

Food Service: The role of the food service portion of this project is to develop and promote state and local adoption of uniform sanitation standards, to provide guidance, training, and technical assistance (direct and through contract), and to evaluate state food protection programs.

The food service function is a cooperative federal/state program covering an estimated 386,000 commercial and 172,000 institutional food service establishments, 165,000 food stores, and 1,069,000 food vending locations.

About 40 percent of the family food budget is spent on meals prepared outside the home. The Centers for Disease Control has reported that where food outbreaks were caused by mishandling of food during 1981, 55 percent of the time the mishandling occurred in food service establishments where meals are prepared for public consumption. In contrast, food processing establishments where food is commercially prepared for market accounted for only two reported outbreaks.

The nation's more than 3,500 state and local regulatory agencies assume primary responsibility for monitoring the retail segments of the food industry, and for providing assurances that industry is adequately protecting the consumer in the marketplace. FDA seeks to promote and maintain a uniformly effective system of state/local regulatory programs nationwide.

Shellfish Safety: The shellfish safety portion of this project is concerned with the development and support of uniform state and foreign shellfish sanitation control programs. Research projects are conducted to evaluate health hazards associated with eating shellfish and to develop improved methods to detect harmful substances in shellfish.

Molluscan shellfish such as oysters, clams, and mussels become contaminated from polluted waters because they have the ability to concentrate pathogenic microorganisms and toxic chemicals from their environment. The increased population in coastal communities and the trend toward industrial development on estuaries continually increase the potential for harmful pollution in shellfish growing areas. Infectious diseases and chemical intoxications may result from the consumption of contaminated shellfish.

Naturally occurring marine biotoxins such as paralytic shellfish poison in shellfish also cause illness and death in humans.

FDA promotes uniform application of health controls by evaluating state programs, publishing a list of certified instate dealers, and providing technical assistance and training to the states.

Milk Safety: The milk safety portion of this project focuses on assuring the nation's milk supply is uniformly safe and wholesome.

The shift in this country from a rural to an urban society has concentrated the population in areas away from the production sources of perishable dairy products, creating special problems in their handling and transportation. To assure the nation's milk supply is uniformly safe and wholesome, the FDA in cooperation with the states, provides sanitation standards for the production and processing of milk and milk products by publishing the Grade A Pasteurized Milk Ordinance (PMO), and administers a voluntary interstate milk shipper certification program designed to provide receivers of these products with reliable data on sources of quality milk.

Sanitation and enforcement ratings given to milk shippers by 50 states are audited by FDA to insure the minimum requirements of the PMO are met in all states. In addition, FDA provides national leadership to state rating and regulatory agencies, as well as to the industry, in milk sanitation activities and technological advances, thus insuring the PMO will be uniformly interpreted by all participants.

Project Mission:

Assure the acceptability of food handling and preparation practices where foods are sold or otherwise provided to consumers, such as institutional and public eating places, food stores, and food vending locations; assure that shellfish are safe for human consumption; and assure that the nation's milk supply is uniformly safe and wholesome.

Applicable Legal Authority:

Applicable Statutes: PHS Act and FD&C Act.

Applicable Sections: Sections 301 and 311 of the PHS Act authorize FDA to sponsor research and investigations and to provide aid to state and local authorities in the enforcement of their health regulations. Section 361 of the PHS Act provides for federal assistance to states in preventing the interstate transmission of disease. Section 401 of the FD&C Act authorizes FDA to set standards of quality. Section 402 of the FD&C Act prohibits the shipment of any adulterated food in interstate commerce.

Project Activities:

Food Service.

- Provide national sanitation standards for food service, food stores and food vending in the form of model codes, and promote their adoption.
- Certify state officials who demonstrate their ability to uniformly conduct establishment inspections and local program evaluations.
- Provide technical assistance, training, seminars, and workshops to assist state food program directors and evaluation officers.
- Evaluate statewide food service protection programs and food chain operations.

Shellfish Safety.

- Promote sanitary control over all phases of shellfish growing, harvesting, processing, and marketing operations.
- Encourage states and foreign countries shipping fresh and frozen shellfish into the U.S. to develop standardized shellfish sanitation control practices.
- Conduct research to assure the safety of shellfish.

Milk Safety.

- Provide sanitation standards for the production and processing of milk and milk products.

- Provide technical assistance to state and local milk regulatory agencies and industry.
- Administer and monitor the Federal/State Cooperative Interstate Milkshippers Certification program.

Project Interaction:

Other Federal Agencies

General Services Administration (GSA): Under an Interagency Agreement, FDA provides assistance to GSA in maintaining acceptable levels of sanitation in GSA-managed food facilities. Services provided include FDA inspections, sample collection and analysis, facility plan review, training, and general consultation.

Department of Transportation (DOT): Under an Interagency Agreement, FDA provides assistance to Federal Aviation Administration (FAA) - Metropolitan Washington Airports in maintaining acceptable levels of sanitation in FAA-managed food facilities at Washington National Airport. Services provided include FDA inspection, facility plan review, training, and general consultation.

Department of Defense; Other Federal Agencies: FDA notifies DOD when a state removes a certified interstate milk shipper from the list of certified shippers. DOD and other federal agencies, such as the Veterans Administration, require the use of certified interstate milk shippers and rely on the list for source selection.

Responsible Contact:

Ralston B. Read, Jr., Ph.D. - Center for Food Safety and Applied Nutrition

Other Contact:

C. Cross - ORA

FOOD ECONOMICS

Program Abstract:

Consumers may be economically harmed through deceptive packaging, insufficient labeling information, false and misleading labeling, nonfunctional slack-fill, and economic adulteration of food items. FDA establishes regulations where necessary to prevent such deception.

FDA develops and/or revises food standards on its own initiative, or in response to petitions from consumer groups, industries, or interested persons to resolve economic problems. Food standards are regulations that define the identity, quality, and/or fill of containers for manufactured foods. Congress authorized FDA to develop food standards that promote honesty and fair dealing in the interest of the consumer. Tea standards are established each year setting the quality, purity, and fitness of the tea to be permitted entry into the United States.

FDA maintains surveillance/compliance for enforcement of food standards, labeling regulations, and nonfunctional slack-fill regulations.

Program Mission:

Assure that the consumer is not economically harmed by misleading labeling or packaging and that product integrity is maintained through the development, promulgation, and enforcement of standards and regulations.

Applicable Legal Authority:

Applicable Statutes: Fair Packaging and Labeling Act; FD&C Act; and Tea Importation Act.

Applicable Sections: Sections 4 and 5 of the Fair Packaging and Labeling Act provide for accurate labeling and fair packaging of food products to facilitate value comparison by consumers.

Sections 301, 402, and 403 of the FD&C Act prohibit the interstate commerce of adulterated foods, and false or misleading labeling of food products. Section 401 authorizes FDA to establish reasonable standards of identity, quality, and fill of container for food

FOOD ECONOMICS

products. In 1946 and 1948, Congressional approval was given for the U.S. government to participate in Food and Agricultural Organization/World Health Organization (FAO/WHO) activities of the United Nations. The State Department concluded in 1962 that this approval covered participation in the development and adoption procedures for international food standards promulgated by the FAO/WHO Codex Alimentarius Commission. The U.S. is obligated to consider each Codex standard for acceptance by this country. Codex standards may be accepted by the U.S. either in whole or in part, only by promulgating new or, when necessary, amending existing U.S. standards for the foods as provided for in Section 401 of the FD&C Act.

The Tea Importation Act authorizes FDA to establish tea quality, purity, and fitness standards based on sample standards for tea prepared by the Board of Tea Experts.

Program Activities:

Develop and/or revise standards for food to ensure identity, quality, and/or fill of container.

- Establish new food standards and/or amend existing ones in response to citizens' petitions.
- Review existing standards as required by the Regulatory Flexibility Act of 1980 (P.L. 96-354), Executive Order 12291, and the Paperwork Reduction Act of 1980 to determine if there is a continuing need for the regulation and propose repeal if justified.
- Evaluate the Codex Alimentarius standards (international food standards) for acceptance by the U.S. and establish new and/or amend existing U.S. standards, as appropriate.
- Revise and update existing standards to require as complete a label declaration of ingredients as is meaningful and as the Act permits.

Investigate potential economic abuses and establish and enforce regulations to prevent or minimize such abuse.

- Investigate consumer and industry complaints of economic adulteration and misbranding and recommend appropriate action.
- Evaluate pattern recognition methods for the determination of adulteration of processed orange juices.

- Continue factory inspections and import examinations to identify and take corrective action against flagrant violations.
- Examine tea offered for entry into the United States for quality, purity, and fitness for consumption.

Project Interaction:

Nutrition: Actions are taken against false and misleading nutritional claims with input from the Nutrition project.

Responsible Contact:

Raymond E. Schucker, Ph.D. - Center for Food Safety and Applied Nutrition

Other Contact:

J. Van Vechten - ORA

PROGRAM RESOURCE SUMMARY
Food Economics¹

Project Title
Food Economics
TOTALS

FY 86 RESOURCES			
Totals		Percent of \$	
FTE	\$ (000)	Program	FDA
64	\$2,875	100%	0.7%
64	\$2,875	100%	0.7%

FIELD/HQ DISTRIBUTION OF 1986 RESOURCES			
FTE		\$ (000)	
FIELD	HQ	FIELD	HQ
33	31	\$1,258	\$1,617
33	31	\$1,258	\$1,617

¹Resources reflect FEA FY 86 President's Budget.

STATION 101 - 102 - 103 - 104			
DATE	TIME	WIND	TEMP.
10/10	10:00	10	10.0
10/11	10:00	10	10.0
10/12	10:00	10	10.0

STATION 105 - 106 - 107 - 108			
DATE	TIME	WIND	TEMP.
10/13	10:00	10	10.0
10/14	10:00	10	10.0
10/15	10:00	10	10.0

STATION 109 - 110 - 111 - 112	
DATE	TIME
10/16	10:00
10/17	10:00
10/18	10:00

COSMETICS

Program Abstract:

Cosmetics are articles applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions. They include eye and facial make-up preparations, hair shampoos and sprays, hair colors, perfumes, deodorants, nail enamels, suntan lotions, shaving creams, dentifrices, and related products.

Cosmetics containing skin irritants or allergens, or pathogenic microorganisms, have been shown to cause topical adverse reactions. Some cosmetic ingredients known to penetrate the skin have been demonstrated in animal tests to cause internal adverse effects. The most publicized examples of cosmetic substances penetrating the skin and likely to present a hazard to public health are certain coal-tar hair dyes, nitrosamines, and dioxane which were found to be animal carcinogens.

To determine the safety of cosmetics, FDA evaluates consumer complaints of cosmetic injuries; develops methods for ingredient identification and analyzes cosmetics; maintains registries of cosmetic establishments, formulations, and consumer adverse reactions, and conducts toxicological and clinical research. FDA also offers consumers and manufacturers guidance on the safe use, testing, and sanitary manufacture of cosmetics. In addition, FDA promulgates regulations to enforce the manufacture of safe and truthfully labeled products, and surveys cosmetic establishments and products to assure regulatory compliance.

Program Mission:

Assure that cosmetic products are safe, truthfully and informatively labeled, and truthfully packaged.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and Fair Packaging and Labeling Act (FPLA).

Applicable Sections: Section 301 of the FD&C Act prohibits the introduction or receipt in interstate commerce of any adulterated or misbranded cosmetic. Section 601 deems a cosmetic to be adulterated if it contains a poisonous or deleterious substance which may cause it to be injurious to health or if it has been manufactured or held under insanitary conditions whereby it may have become harmful to consumers. Section 602 deems a cosmetic to be misbranded if its labeling is false or misleading, does not bear the required labeling information, or is not truthfully packaged. Unlike food additives and new drugs, there is no statutory requirement that a cosmetic product or ingredient be proven safe before introduction into interstate commerce.

Section 4 of the FPLA requires the package label to bear the product identity, the name of the manufacturer or distributor, and the net quantity of contents. Section 5 authorized the promulgation of regulations requiring mandatory ingredient labeling.

Program Activities:

Conduct scientific research to determine the safety of cosmetics and identify hazardous ingredients.

- Conduct studies to develop predictive methods for the determination of the adequacy of preservation of cosmetics; to obtain data on the irritation, sensitization, and skin penetration of cosmetic substances; and to develop analytical, microbiological, and toxicological methods for the determination of hazardous ingredients or microorganisms.

Maintain registries for the voluntary filing of cosmetic manufacturing establishments and formulations, and for industry and consumer reporting of adverse reactions.

- Maintain registries of cosmetic manufacturing establishments, raw materials and formulations for the identification of manufacturers' products violating regulatory requirements.
- Maintain the voluntary industry reporting program of consumer complaints of adverse reactions to cosmetics and the program of compiling adverse reaction information received directly from consumers. Review and evaluate the voluntarily submitted product formulations and adverse reaction data for health hazard implication.

Maintain surveillance of cosmetic establishments and products to ensure compliance with regulatory requirements.

- Inspect cosmetic establishments to determine that facilities are sanitary and that products are prepared, packed, or held in accordance with good manufacturing practices. Collect samples for evaluation.
- Evaluate samples collected during establishment inspections and samples from consumer complaints, for the presence of hazardous ingredients, microbial contamination, and dermal or ocular toxicity, as well as for compliance with labeling requirements.

Provide consumer and industry guidance.

- Inform consumers and cosmetic manufacturers about the safe use, toxicological and microbiological testing, sanitary manufacture, and regulatory requirements respecting cosmetics.

Support regulatory activities to ensure that cosmetics are safe and properly labeled.

- Recommend regulatory action against products determined to contain hazardous ingredients or pathogenic microorganisms.
- Support surveillance activities to ensure compliance with cosmetic labeling requirements, particularly the declaration of ingredients and the statement of appropriate warnings.
- Promulgate regulations for the efficient enforcement of the cosmetic provisions of the FD&C Act and the FPLA.

Responsible Contact:

Heinz J. Eiermann - Center for Food Safety and Applied Nutrition

Other Contact:

J. Van Vechten - ORA

...to ensure

...in accordance

...and industry

...that

...

...

...

...

...

PROGRAM RESOURCE SUMMARYCosmetics¹

Project Title
Cosmetics
TOTALS

FY 86 RESOURCES			
Totals		Percent of \$	
FTE	\$ (000)	Program	FDA
56	\$2,792	100%	0.7%
56	\$2,792	100%	0.7%

FIELD/HQ DISTRIBUTION OF 1986 RESOURCES			
FTE		\$ (000)	
FIELD	HQ	FIELD	HQ
17	39	\$659	\$2,133
17	39	\$659	\$2,133

¹Resources reflect FDA FY 86 President's Budget.

HUMAN DRUGS AND BIOLOGICS

Program Abstract:

Under the Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act), FDA has national responsibility for the regulation of biologics and drugs intended for human use.

FDA is responsible for regulating the testing of Investigational New Drugs (INDs) and biologics and for approving or disapproving applications for marketing of new drugs and biologics--New Drug Applications (NDAs) for drugs, and licenses for biologics. FDA also monitors the quality of products manufactured in or imported into the U. S. Other responsibilities include collecting and evaluating information on adverse effects experienced with marketed products, regulating the advertising and promotion of prescription drugs and biologics, and establishing and monitoring standards for use, labeling, and composition of biologics and drugs. FDA also disseminates timely and accurate product information to the medical community and the public, identifies drugs which have potential for abuse, and makes recommendations to the Drug Enforcement Agency (DEA) for drug classification and control.

FDA's responsibility is discharged through such primary activities as the review of research and manufacturing data provided by sponsors and applicants, and compliance activities, such as establishment registration and product listing, establishment inspections, sample examinations, and related corrective regulatory action where violations of the FD&C Act, the PHS Act, or regulations are observed.

FDA continues to improve the review process for drug applications by revising requirements and applying efficient management techniques. Increased involvement of highly qualified experts in the fields of medicine and related areas of science also contributes to applications evaluation. Recent major breakthroughs in pharmaceutical research and technology promise important new medical therapies. One of FDA's major objectives is to expand its scientific capabilities to respond and contribute to these advances. The Agency continues to recruit scientists with special training and expertise, and has developed and maintains a core staff of scientists who, through continuing professional development, training, and conduct of research activities, are able to interact effectively with industry and academic counterparts in biomedical research and product development. Thus the scientific review of drug and biologic products is conducted by scientists who are directly involved in developing pharmaceutical technologies. Activities include intramural and extramural research in basic scientific processes and health problem areas, and development of new standards such as bioequivalence requirements for drug products.

Regulatory activities are supplemented by the review of literature and experience reports submitted by industry and the medical profession for potential or real safety and efficacy problems. FDA monitors preclinical and clinical investigations to ensure that the research data provided in support of applications are properly obtained and reliable and that risk to experimental human subjects is minimized. Also, emphasis continues on ensuring the highest possible quality of products on the market and improving the dissemination of important information. FDA's biologic and drug quality assurance program focuses both on the quality of products and on the compliance of the manufacturer with the standards established in the Current Good Manufacturing Practice (CGMP) regulations. Special emphasis is placed on actions against fraudulent drug and biological products to protect consumers from products that represent indirect health hazards and major economic fraud. Another important task for FDA is upgrading the content of prescription drug labels to reflect the most current knowledge related to drugs to assist in their safe and effective use.

Program Mission:

Assure that all drug and biologic products used for the prevention, diagnosis, and treatment of disease are safe and effective and that information on proper use is available to all users.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and PHS Act.

Applicable Sections: Chapter V of the FD&C Act states that a new drug must be reviewed for safety and efficacy before marketing. The chapter authorizes FDA to regulate the clinical testing, manufacturing, distribution, and marketing of drugs. It also authorizes FDA to regulate prescription drug advertising, to register all regulated drug establishments, and to list all drugs commercially marketed in the U.S. Under Section 301 of the PHS Act, FDA provides information and coordination services for the Poison Control Program as authorized by the Surgeon General. Section 351 of the PHS Act authorizes FDA to license biological products and manufacturing establishments.

Program Activities:

- Evaluate the safety and effectiveness of drugs and biologics before permitting marketing; monitor preclinical and clinical testing of new drugs and biologics.
- Review all drug products (prescription and over-the-counter) marketed originally between 1938 and 1962 to ensure that all are effective as well as safe and not misbranded.

- Develop and publish monographs for monitoring over-the-counter drug products on the market.
- Issue licenses to manufacturing establishments including plasmapheresis centers, blood banks, vaccine producers, and others; issue licenses for biological products.
- Monitor the quality of marketed products through surveillance and compliance actions; conduct inspections of licensed and unlicensed biological manufacturing establishments to ensure compliance with established regulations and good manufacturing practices and remove those products from the marketplace not meeting standards, including health fraud products.
- Conduct research to establish product standards and develop analytical methodology and improved testing methods.
- Conduct potency and safety tests of licensed biological and insulin products before they are released for marketing.
- Collect and evaluate information on marketed products and adverse reactions to support the updating of standards and regulatory decisionmaking.
- Disseminate drug information to the medical community and the public, including development and implementation of labeling standards and a revision program.
- Monitor product advertisements and promotional labeling, and enforce requirements for accurate and balanced representations.
- Support the national Poison Control Program and regulate methadone treatment programs.
- Register annually all regulated manufacturing and blood banking establishments; maintain a listing of all drug and biological products commercially marketed in the U.S.

Responsible Contact:

Harry M. Meyer, Jr., M.D. - Director, Center for Drugs and Biologics

PROGRAM RESOURCE SUMMARY
Human Drugs and Biologics¹

Project Title	FY 86 RESOURCES			FIELD/HQ DISTRIBUTION OF 1986 RESOURCES			
	Totals		Percent of \$ (000)	FTE		\$ (000)	
	FTE	\$ (000)		FIELD	HQ	FIELD	HQ
Bioresearch Monitoring: Drugs and Biologics	175	\$8,318	6.5%	101	74	\$4,364	\$3,954
Generic Drug Evaluation	131	8,626	6.7	13	168	558	8,068
Prescription Drug Advertising and Labeling	32	1,703	1.3	0	32	0	1,703
Biopharmaceutics	81	4,330	3.4	17	64	726	3,604
Drug Experience and Trends Analysis	65	4,928	3.8	0	65	0	4,928
Drug Quality Assurance	757	35,423	27.5	567	190	24,435	10,988
Generic Drug Standards	95	4,337	3.4	76	19	3,285	1,052
New Drug Evaluation	504	27,491	21.4	30	474	1,236	26,255
Over-the-Counter Drug Evaluation	86	4,328	3.4	9	77	383	3,945
Bacterial and Allergenic Products	93	5,560	4.3	1	92	45	5,515
Blood and Blood Products	199	12,239	9.5	52	147	2,262	9,977
Viral and Rickettsial Products	119	9,528	7.4	0	119	0	9,528
Health Fraud: Human Drugs and Biologics	40	1,847	1.4	30	10	1,282	565
TOTALS²	2,427	\$128,658	100%	896	1,531	\$38,576	\$90,082

¹Resources reflect FDA FY 86 President's Budget.

²Totals do not include insulin and color certification funding which are reimbursable.

Table 1: Summary of Data			
Year	Value 1	Value 2	Value 3
1990	100	200	300
1991	110	210	310
1992	120	220	320
1993	130	230	330
1994	140	240	340
1995	150	250	350
1996	160	260	360
1997	170	270	370
1998	180	280	380
1999	190	290	390
2000	200	300	400

Table 2: Detailed Data			
Year	Value 1	Value 2	Value 3
1990	100	200	300
1991	110	210	310
1992	120	220	320
1993	130	230	330
1994	140	240	340
1995	150	250	350
1996	160	260	360
1997	170	270	370
1998	180	280	380
1999	190	290	390
2000	200	300	400

Table 3: Additional Data			
Year	Value 1	Value 2	Value 3
1990	100	200	300
1991	110	210	310
1992	120	220	320
1993	130	230	330
1994	140	240	340
1995	150	250	350
1996	160	260	360
1997	170	270	370
1998	180	280	380
1999	190	290	390
2000	200	300	400

Bioresearch Monitoring: Drugs and Biologics

Project Abstract:

The premature marketing of a number of inadequately tested drugs was one of the factors that led to the passage of the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic (FD&C) Act. The 1962 Amendments and the 1963 Investigational Drug Regulations provided FDA with the authority to exercise a much closer control over the preclinical and clinical testing of investigational drugs.

In evaluating the safety and effectiveness of new drugs and biologics, FDA must rely on data obtained by nonclinical and clinical investigators selected by the sponsors to conduct studies on the products in question. Well-conducted trials are essential to proper decision-making on drug safety and efficacy. Incompetently conducted trials and the submission of false data place the subjects exposed to new drugs and biologics at unnecessary risk and confound judgments on safety and effectiveness. Therefore, in addition to reviewing data submitted by the sponsor, FDA must ensure that those data are properly obtained and are reliable, and that the rights and welfare of human research subjects are protected. FDA promulgates and keeps current regulations and guidelines, inspects and evaluates research through surveillance/compliance programs, and develops educational programs to provide guidance to the research community.

Regulations published pursuant to the Controlled Substances Act (Comprehensive Drug Abuse Prevention and Control Act of 1970), require annual registration of narcotic treatment programs with the Drug Enforcement Administration (DEA). This registration is dependent upon a determination by the Secretary of HHS that applicants for these programs are qualified to engage in the treatment of narcotic addiction, based upon the narcotic treatment standards established by the Secretary, and that approved narcotic treatment programs are in compliance with these standards. Through inspections, FDA determines the compliance status of drug abuse treatment programs for annual registration with DEA and for continued FDA approval. Methadone, a synthetic narcotic drug, is the only drug approved by FDA for the detoxification and/or the maintenance treatment of narcotic addiction.

Project Mission:

Assure that nonclinical and clinical investigations are conducted in a scientific manner that will afford protection to human subjects participating in clinical trials and will produce valid bioresearch data.

Assure that practices of narcotic treatment programs comply with federal regulations which establish standards for registration and treatment of narcotic addiction.

Applicable Legal Authority:

Applicable Statutes: FD&C Act, Comprehensive Drug Abuse Prevention and Control Act of 1970 (CDAP&C Act), and Narcotic Addict Treatment Act of 1974 (NATA).

Applicable Sections: Section 301 (e), 505 (i) and (j), and 704 of the FD&C Act; Section 4 of Title I and Section 201 of Title II of the CDAP&C Act; and Section 3 of the NATA (Public Law 93-281).

Project Activities:

Develop regulations and guidelines.

- Develop regulations and guidelines applicable to the conduct of nonclinical and clinical investigations (e.g., good laboratory practices, safeguards for human subjects, etc.) and to narcotic treatment programs.
- Evaluate the effectiveness of existing regulations and guidelines, and make revisions or additions as necessary.

Conduct monitoring and evaluation programs to ensure the quality and integrity of bioresearch data.

- Implement continuing compliance programs for inspections selected for routine surveillance or prompted by referral or questions raised during drug application review. Inspections will be conducted of:
 - a) clinical investigations (commercially and independently sponsored);
 - b) institutional review boards charged with the responsibility for protecting subjects in new drug and biologics studies;
 - c) radioactive drug research committees;
 - d) nonclinical laboratories;
 - e) commercial sponsors and their monitors; and
 - f) laboratories conducting bioavailability and bioequivalency studies.

- Review information generated by surveillance and compliance inspections to evaluate the need for regulatory follow up. Evaluate recommendations for legal actions, and initiate and manage such activities as necessary.

Evaluate applications for use of methadone in the treatment of narcotic addiction by hospitals and narcotic treatment programs.

- Review applications and approve those which comply with the narcotic treatment standards, 21 CFR 291.505, Conditions for Use of Methadone.
- Review and evaluate all active narcotic treatment program applications for which submissions of updated information are received to ensure that applicants continue to meet the requirements upon which approval was granted.
- Review, evaluate and approve or deny individual patient exceptions and program exemptions to the narcotic treatment standards.
- Consult DEA concerning the approval status of all applications for registration as narcotic treatment and hospital detoxification programs.

Monitor and inspect narcotic treatment programs to determine compliance with the narcotic treatment standards.

- Review and evaluate all narcotic treatment program inspection reports for compliance with the standards.
- Initiate procedures to suspend or to revoke the Drug Enforcement Administration registration of narcotic treatment programs which fail to comply with the standards.
- Disseminate information concerning the compliance status of narcotic treatment programs to the state authorities, DEA, NIDA, and other federal agencies.

Conduct education and information programs.

- Disseminate data derived from surveillance and compliance inspections as an educational aid to sponsors, investigators, institutional review boards, and other segments of the research community.

Project Interaction:

New Drug Evaluation: The NDE project identifies important clinical and nonclinical studies supporting drug and biologics applications for surveillance and data audit inspections. This project also identifies suspect clinical or nonclinical studies or possible inadequacies in subject protection procedures for follow up by the Bioresearch Monitoring project.

Biopharmaceutics: This project provides specialized support to the Bioresearch Monitoring project in monitoring commercial testing facilities that conduct bioequivalence studies.

Over-the-Counter (OTC) Drug Evaluation: Scrutiny of studies by OTC Drug Monograph branches may identify studies for audit by the Bioresearch Monitoring project to determine quality of data and adherence to human subject protection regulations.

Bacterial and Allergenic Products, Blood and Blood Products, Viral and Rickettsial Products: The mission of the Bioresearch Monitoring project is to assure the quality and integrity of bioresearch data submitted to these projects.

Animal Drugs; Bioresearch Monitoring; Food Additives; Medical and Radiological Device Monitoring and Quality Conformance; Medical and Radiological Device Product Evaluation: These projects are part of the Agency-wide bioresearch program.

Drug Experience and Trends Analysis: The DETA project collects and provides adverse reaction data related to the use of methadone.

Other Federal Agencies

National Institute on Drug Abuse (NIDA): The FDA and NIDA jointly published revised narcotic treatment standards which became effective November 18, 1980. FDA and NIDA operate under a Memorandum of Understanding which describes the cooperative relationship and procedures relative to the implementation of the narcotic treatment standards.

Drug Enforcement Administration (DEA): The Narcotic Treatment Standards incorporate the security and recordkeeping requirements of the Controlled Substances Act of 1970 (CSA). Additionally, the Narcotic Addict Treatment Act of 1974, which amends the CSA, requires that narcotic treatment programs be registered with the DEA. Such registration is dependent upon a determination by FDA that these programs meet the standards established by the Secretary of HHS.

Consumer Product Safety Commission (CPSC): The Narcotic Treatment Standards incorporate a requirement from the regulations of the Consumer Product Safety Commission that methadone for take-home purposes be dispensed in containers with safety closures.

Responsible Contacts:

Sam T. Gibson, M.D. - Center for Drugs and Biologics

Other Contact:

E. Brisson - ORA

Generic Drug Evaluation

Project Abstract:

The Food, Drug, and Cosmetic (FD&C) Act of 1938 required that all drugs be approved for safety before marketing. In 1962 the Act was amended to require that effectiveness for the drug products' claims be demonstrated before approval, and that drug products approved for safety only, from 1938 to 1962, also be evaluated for effectiveness. Either approved New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) are required for marketing of these drugs. The DESI (Drug Efficacy Study Implementation) program was established in 1968 to assure that the drug products approved between 1938 and 1962 either demonstrate effectiveness for their claims and had approved applications, or be withdrawn from the market. Shortly thereafter it became apparent that many products identical, similar, or related to the DESI drugs were being marketed without approval and without the substantiating data establishing their safety and efficacy. As a result, the ANDA program was established in 1972 to assure that generic drug products related to effective DESI products were also safe, effective and properly labeled. The Drug Efficacy Study product review, started in 1966 by the National Academy of Science/National Research Council (NAS/NRC), classified the drug products under review as to their degree of effectiveness. NAS/NRC recommendations were reviewed by FDA scientists and determinations of the effectiveness of the claims were published in the Federal Register.

In 1984, the Drug Price Competition and Patent Term Restoration Act of 1984 amended the FD&S Act to allow ANDAs for drug products first approved after 1962.

Initial FDA decisions on the indications for use of all 3,443 drug products in the study were completed and published by 1974. Under the DESI program, final actions on approximately 99 percent of the 1938--1962 marketed drugs (DESI products) have been completed. In 1980 FDA was committed through a litigation settlement to publish conclusions on the remaining DESI products--one half by June 1982 and the rest by September 17, 1984. The first goal was met, and FDA substantially met the second goal, that is, as of the target date only 39 products covered by the court order remained subject to further action to resolve their effectiveness. The court-established timetable does not apply to DESI-type actions for "related" drug products, nor are hearings that are granted and to be held, included. Such DESI activities will continue in FY 1986.

With completion of most of the DESI program, emphasis has been shifting to the ANDA program. ANDAs are accepted by FDA for drug products identical to, acceptably similar to, or related to the drug products in the Drug Efficacy Study which have been judged to have effective indications and have been published in the Federal Register as being acceptable as ANDAs. To obtain approval of ANDAs, the

manufacturers must not only meet all requirements of the application, but must also be in compliance with the Current Good Manufacturing Practice (CGMP) regulations. The drug products' manufacturing processes and testing procedures must also be validated.

Project Mission:

Assure that all prescription drugs initially approved for marketing between 1938 and 1962 on the basis of safety are reviewed and evaluated for efficacy; that generic revisions of drug products found to be effective (DESI pre-62 products) and those found to be safe and effective (approved post-62) meet appropriate abbreviated application approval requirements; and that drug products are removed from the market when evidence of effectiveness is lacking or when products are marketed without an approved ANDA or NDA.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Section: Section 505 requires FDA to withdraw approval of NDAs if there is lack of substantial evidence supporting efficacy for the conditions of use prescribed, recommended, or suggested in the labeling. Section 505 was amended in 1984 to set forth specific requirements for abbreviated applications. The Supreme Court has held that FDA's decision on products that have new drug approval is applicable to generic (me-too) products provided requisite procedures are observed to safeguard the firm's rights.

Project Activities:

Evaluate efficacy data for possible reclassification of drugs or indications initially judged less-than-effective and publish conclusions.

- Review results of clinical studies submitted by manufacturers in response to DESI announcements in the Federal Register and publish conclusions: issue Notices of Opportunity for Hearing; grant and hold hearings; issue Final Orders upgrading the drug products or indications, or denying the hearings; and issue summary judgments.

Review ANDAs for appropriate action.

- Review ANDA submissions for effective identical or acceptably related generic drug products and take appropriate action. (Efficacy data are not required, but quality control information, proposed labeling, and bioavailability/bioequivalence data are required, as well as Establishment Inspection Reports or CGMP Profile Status Reports.)

- Perform and evaluate pre-approval, on site establishment inspections to monitor the manufacturing process, including compliance with CGMP regulations or review of the firm's CGMP profile.

Remove from the market drug products in the Drug Efficacy Study judged to have no indication higher than "ineffective."

- Continue nationwide compliance activities to follow up and remove from the market those "ineffective" drug products which have had a Final Order published withdrawing approval of the NDA.

Continue nationwide compliance activities to ensure appropriate action on marketed generic drug products that are identical, related, or similar to NDA drug products.

- Identify and remove from the market those drug products that are identical, related, or similar to reviewed drugs judged "ineffective." Identify and remove from the market, in established priority sequence, those drugs without approved NDAs or ANDAs and which are identical, related, or similar to reviewed drug products judged to have effective indications.
- Utilize the Drug Listing data to aid in identifying generic drug products subject to the efficacy evaluations.

Evaluate data and arguments offered by firms in support of their requests for hearings and publish conclusions.

- Review and evaluate hearing requests (for DESI drug products and "related" drug products) supported by data and arguments submitted by the manufacturers of drug products published as "ineffective" with Notices of Opportunity for Hearing on the question of whether these drugs should be removed from the market. Hold hearings or deny hearing requests and publish findings and conclusions on efficacy.

Complete evaluation of Paragraph XIV drugs.

- Review data submitted for those remaining drug products for which the court allowed an extension of time for such required studies, publish conclusions when reviews of the studies are completed, and remove noncomplying products from the market.

Project Interaction:

Biopharmaceutics: The Biopharmaceutics project reviews study protocols and bioavailability and bioequivalence data for ANDAs when these are required, and provides advice on any biopharmaceutical problems relating to DESI drugs.

Drug Quality Assurance: The DQA project provides data to be utilized in identifying those prescription drug products that meet or fail to meet the requirements of DESI drugs, NDAs or ANDAs, thereby identifying those products that require regulatory activities. In addition, insulin certification activities are affected by DESI program effectiveness and labeling activities.

New Drug Evaluation: The NDE project provides medical and scientific information needed to evaluate DESI drugs and ANDAs.

Over-the-Counter Drug Evaluation: The OTC Drug Evaluation project provides evaluations of data submitted for OTC drug categories that pertain to DESI drug products, especially in the cough/cold/allergy areas, and for other DESI drug products recommended to be switched from prescription to OTC status.

Prescription Drug Advertising and Labeling: The labeling revision program is affected by DESI labeling activities.

Responsible Contact:

Kent T. Johnson - Center for Drugs and Biologics

Other Contacts:

D. Read - CDB
A. Lavender - CDB
R. Temple, M.D. - CDB
M. Seife, M.D. - CDB
B. Chism - ORA

Prescription Drug Advertising and Labeling

Project Abstract:

The Food, Drug, and Cosmetic (FD&C) Act of 1938, as amended, requires that prescription drugs be safe, effective, and properly labeled; the 1962 Drug Amendments made prescription drug advertising subject to FDA regulation to ensure that it provides adequate directions for use and presents a balanced picture regarding the benefits versus the adverse effects of the drug.

The labeling is the officially recognized source of information for each marketed prescription drug, and it must accurately reflect the most recent information available in a format and style that is useful to practicing physicians and other health professionals. FDA actively strives to improve labeling practices. New standards are developed, such as those specifying more precisely the contents and scope of labeling, and labels are revised to meet those standards. New types of labeling presentations are investigated and implemented, including class labeling, to present the relative benefit/risk factors of closely related drugs.

For some prescription drugs, it may also be essential that the consumer or patient be advised directly of critical information. As with oral contraceptives and estrogens, FDA develops, tests, and makes available guidelines for package inserts for this purpose.

FDA monitors prescription drug advertisements, promotional labeling, and promotional activities. FDA also issues guidance materials and consults with industry to prevent problems from occurring or reoccurring. FDA is currently gathering information and formulating policy for regulation of new forms of drug promotion, including direct-to-consumer advertising in both electronic and print media, and the use of electronic media (including cable TV) for advertising to professionals.

Project Mission:

Assure that marketed prescription drugs are labeled with the latest information for safe and effective use, that such labeling is presented and distributed in the most effective way, and that prescription drug advertising and promotion is accurate, truthful, and balanced.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and PHS Act.

Applicable Sections: Sections 502, 503, 505, 507, and 701 of the FD&C Act cover misbranding of drugs, exemptions, new drugs, certification of antibiotics, and regulations and hearings; and Section 351 of the PHS Act covers biological products.

Project Activities:

Continue implementation of the Labeling Revision program to upgrade all prescription drug labels/package inserts to current standards, develop class labels, and evaluate generic drug labels.

- Continue revision of new labeling standards for the content and format of package inserts.
- Implement the professional Labeling Revision program as proposed in the compliance schedule published in the Federal Register.
- Develop and publish class labeling for selected drugs and evaluate the feasibility of further class labeling development.
- Provide guidance to FDA medical reviewers for labeling revisions and for guidelines and/or regulations revisions.
- Develop a labeling revision plan for all remaining drugs not covered by class or generic labeling.

Define policy issues and evaluate alternative approaches for patient education programs on prescription drugs.

- Conduct research on patient understanding and needs for prescription drug information.
- Continue to solicit and evaluate consumer and health professional input to FDA policy via meetings, publications, and Federal Register announcements, and evaluate existing patient education materials.
- Develop and implement official patient labeling for drugs that require labeling for their safe use.

Provide guidance to the divisions in the Office of Drug Research and Review and the Office of Biologic Research Review and to the Division of Generic Drugs to ensure quality, consistency, and timeliness in the labeling of drugs during pre- and post-marketing periods.

Monitor prescription drug advertisements and promotional labeling.

- Monitor prescription drug advertisements, promotional labeling, and advertising campaigns including journals, newspapers, books, films, other audiovisual materials, use of electronic media exhibits, etc.
- Review and monitor Continuing Medical Education activities sponsored by the pharmaceutical industry including course materials mailed to physicians, and seminars, lectures, etc., at conventions and other locations.
- Initiate administrative and/or legal action to remedy violative advertisements or promotional labeling arising from complaints or from monitoring.
- Review package inserts for statements that could lead to improper promotional claims.
- Process New Drug Application supplements with regard to advertisements and promotional labeling submitted under the requirements of 21 CFR 314.80(b)(3).

Issue guidance materials and consult with industry to prevent problems from occurring and reoccurring.

- Participate in industry seminars and workshops, publish articles, distribute guidelines from FDA publications, etc., to promote understanding of advertising requirements and to encourage voluntary compliance.
- Formulate policy and develop new guidelines or regulations regarding prescription drug advertising.
- Conduct meetings to negotiate administrative remedial actions with drug firms and advertising sponsors. Develop and recommend specific remedial instruments applicable to specific violative situations.
- Conduct informal citation hearings under Section 305 of the Act in areas of advertising.

Project Interaction:

Biopharmaceutics: The BIO project conducts reviews on the pharmacokinetic sections of labeling for appropriate drugs.

Generic Drug Evaluation: DESI drug labeling is included in the labeling revision program.

Drug Experience and Trends Analysis: The DETA project performs reviews of the Adverse Reaction and Overdosage sections of labeling for appropriate drugs.

Drug Quality Assurance: The DQA project provides up-to-date inventories of drugs for the management of the Labeling Revision program.

New Drug Evaluation: The NDE project performs technical reviews for revisions in labeling and reviews selected advertisements and promotional labeling for medical content. The NDE project is provided support through review of proposed package insert labeling for "approvable" new drugs.

Over-the-Counter Drug Evaluation: The OTC project contributes and/or receives labeling guidance on products that represent overlap between prescription drugs and OTC drugs, and shares experiences gained in consumer education with reference to labeling for patients.

Responsible Contacts:

Lloyd G. Millstein, Ph.D. - Center for Drugs and Biologics
Kenneth R. Feather - Center for Drugs and Biologics

Other Contacts:

N. Abel - CDB
B. Chism - ORA

Biopharmaceutics

Project Abstract:

FDA has established a Biopharmaceutics project to address both the bioavailability and bioequivalence areas of drugs. The bioavailability of a drug refers to the amount of active drug substance which becomes systemically available to achieve its therapeutic action. If too much active drug substance were unexpectedly introduced systemically, it could lead to toxic or adverse reactions, whereas deficient levels could cause an inadequate therapeutic response.

Studies from within, as well as outside the Agency, have documented that some drug products with identical active ingredients (generic drugs) may not produce the same systemic levels (i.e., they are not bioequivalent). The systemic drug levels achieved by generic and innovator drug products should not vary from batch to batch within the same brand or from brand to brand.

Under this project, FDA develops bioavailability guidelines; reviews and evaluates pharmacokinetic protocols for possible labeling revision; and studies new chemical entities and dosage forms in Investigational New Drugs (INDs), New Drug Applications (NDAs), and Antibiotic Form 5s.

Abbreviated New Drug Applications (ANDAs), "paper" NDAs, and Antibiotic Form 6s are reviewed to ensure the bioequivalence of appropriate generic drugs. Through intramural and extramural research programs, the Agency develops necessary methodology (such as for dissolution testing, appropriate study design, assays, animal model testing, etc.) for establishing biopharmaceutic performance specifications and for determining drug bioequivalence.

In addition to methodology development, laboratory activities include the testing of products suspected of having biopharmaceutic problems, and fundamental research on formulation and developmental factors which may cause biopharmaceutic problems in the final dosage form.

Project Mission:

Develop biopharmaceutic specifications, policies, and procedures for new chemical entities and generic drugs which can serve as guidelines to drug firms for satisfying new requirements. The guidelines also support drug application submissions as well as serve as the basis for Agency regulatory action when those specifications are not met.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Sections 501-511 authorize FDA to regulate the manufacturing of all marketed drugs, and the investigation and marketing of new drugs through the Investigational New Drug Application (INDA) and NDA processes.

Project Activities:

Perform all biopharmaceutics reviews.

- Establish biopharmaceutic policies and guidelines for drug application submissions and their review.
- Review bioavailability protocols and studies associated with INDAs, NDAs, ANDAs, and Form 5s and 6s for antibiotic drug products.
- Review generic drugs, including Drug Efficacy Study Implementation (DESI) drugs and old drugs, to determine the need for bioavailability/bioequivalence testing.

Plan and implement an integrated FDA biopharmaceutics research and development program utilizing extramural contracts and intramural resources.

- Carry out human in vivo studies to identify bioavailability/bioequivalence problems, and to address issues related to specialized dosage forms, special populations, and other such involved pharmacokinetic areas.
- Continue to develop in vitro tests which correlate with in vivo bioavailability data.
- Carry out a research program to improve in vitro dissolution test methodology and equipment.
- Develop and validate new dissolution methods for introduction as official Agency or compendial methods.
- Continue to establish pharmacological and physiological parameters, indicating drug product performance comparisons where methodology to determine drug sera levels is not available.
- Initiate and perform comparative pharmacokinetic studies using animal models to minimize or eliminate the need for human subjects and to reduce drug study expense.

Document drug classes which have bioequivalence problems, and establish performance standards to be met to satisfy bioequivalence requirements.

- Publish proposals and Final Orders imposing bioequivalence requirements for specific dosage forms for about 100 active ingredients; establish bioequivalence requirements for less-than-effective DESI drugs raised to effective status.
- Support the Department's Maximum-Allowable Cost program for generic drugs by identifying existing or potential bioavailability issues which will need resolution before a drug can be included in that program.

FDA Therapeutic Equivalence List.

- The Division of Bioequivalence Review provides a therapeutic equivalence determination on multisource FDA approved prescription drug products.

Surveillance/compliance program.

- Perform biopharmaceutics tests in support of compliance and litigation activities.
- Conduct industry-wide dissolution surveys on specific generic drugs to compare the dissolution rates between products, as a basis for identifying drugs and drug products which have a high potential for bioequivalence problems.
- Evaluate drug performance data to decide whether or not to recommend compliance action against specific drug products.

State drug lists of acceptable generic drugs.

- Determine the therapeutic equivalence status of drug products for substitution purposes under state drug laws, based on bioavailability/bioequivalence considerations.

Project Interaction:

Generic Drug Evaluation; New Drug Evaluation: The Biopharmaceutics project performs all necessary pharmacokinetic and biopharmaceutic reviews for NDAs, ANDAs, INDs, and Antibiotic Form 5s and 6s; also reviews study protocols; develops dissolution methods for assuring lot-to-lot uniformity of oral antibiotic drugs; and determines whether bioequivalence requirements will be necessary for a particular active ingredient, dosage form, and strength.

Drug Quality Assurance: The Biopharmaceutics project establishes biopharmaceutic specifications as a basis for compliance regulatory actions and evaluates drug performance data to determine the need to recommend to DQA that action be taken against a particular drug product.

Prescription Drug Advertising and Labeling: The Biopharmaceutics project contributes reviews on the pharmacokinetic sections of labeling for appropriate drugs.

Over-the-Counter Drug Evaluation: The Biopharmaceutics project identifies OTC drug active ingredients which may present bioequivalence/bioavailability problems and which need special attention in OTC drug monographs.

Bioresearch Monitoring: Drugs and Biologics: The Biopharmaceutics project provides specialized support and guidelines for the monitoring of commercial testing facilities which conduct bioavailability studies.

Responsible Contact:

Jerome P. Skelly, Ph.D. - Center for Drugs and Biologics

Other Contacts:

B. Chism - ORA
V. Prasad, Ph.D. - CDB
S. Dighe, Ph.D. - CDB
D. Hare - CDB
V. Shah, Ph.D. - CDB
C. Viswanathan, Ph.D. - CDB
N. Malinowski, Ph.D. - CDB

Drug Experience and Trends Analysis

Project Abstract:

FDA collects postmarketing adverse drug and biological experience and utilization data and applies this information to benefit/risk decisions on marketed prescription and over-the-counter (OTC) drugs and biologics. This is necessary because low incidence adverse drug experiences cannot be detected in the small populations used for clinical studies, and such factors as patient age, other disease status, and drug interactions cannot be assessed fully prior to marketing. As a result, manufacturers are required by law to submit drug experience reports. In addition, hospitals and physicians voluntarily submit drug experience reports through direct encouragement by FDA. FDA also actively funds various outside organizations that conduct drug epidemiological studies and maintain registries of adverse effects. Some of these studies enable the Agency to determine not only what drug experiences are occurring, but provide an estimate of either the incidence or the relative risk of a particular adverse effect.

FDA also collects data regarding drug utilization, and develops trends on specific drug uses. Analysis of drug use and trends alerts the Agency to possible abuse, incorrect selection, overuse, or underuse of medication; the denominator data provide estimates of potential drug exposures and can be used for comparing relative market share to relative share of adverse reactions. FDA also collects and analyzes epidemiological data on poisonings and other nonmedical use of marketed drugs.

FDA uses the drug experience information in its continuing evaluation of the adequacy of labeling of drugs and their effective and safe use. Pertinent information is disseminated to health-care professionals to alert them to possible drug reactions.

Project Mission:

Monitor the short- and long-term effects of marketed drugs and biological products, including their utilization, to discover potential safety problems and establish a scientific basis for regulatory actions. Support the new drug review process by maintaining comprehensive data on drug safety. Collect and analyze poisoning case data from centers and other sources to decrease the incidence and severity of injuries and the frequency of deaths from acute poisonings.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and PHS Act.

Applicable Sections: Sections 505 and 507 of the FD&C Act authorize FDA to monitor new drug experience and require drug manufacturers to submit periodic drug experience reports to FDA. The Act further authorizes the Agency to revoke approval of new drugs when monitoring shows that the drugs do not have a favorable benefit-to-risk relationship. Under Section 301 of the PHS Act, FDA is mandated to collect, evaluate, and disseminate data based on reports received from Poison Control Centers.

Project Activities:

Monitor drug and biological experience reports submitted directly to FDA or available to FDA through contracts or other programs.

- Act as focal point for receipt of drug and biologic experience reports from manufacturers and health professionals.
- Process, evaluate, and computerize current drug and biological product experience reports.
- Evaluate current medical literature for reports of new drug experience.
- Publicize and stimulate interest and participation in FDA drug experience programs through direct dialogue with the medical community at major health professional meetings.
- Review and evaluate drug and biologic experience reports received from Tissue Registry of Drugs of the Armed Forces Institute of Pathology, World Health Organization (WHO) International Drug Monitoring Program, Registry of Eye Reactions, and Registry of Dermatologic Effects.
- Apply epidemiological techniques to test hypotheses relating drugs (or biologics) to adverse reactions.
- Continue support of the Boston Collaborative Drug Surveillance Program; the Health Information Designs for Michigan and Minnesota Medicaid Program; Drug Epidemiology Unit for Case-Control Study and Pediatric Inpatient Program; the Mayo Clinic; University of Pennsylvania and Vanderbilt University Medical School. These cooperative agreements provide the necessary data and/or expertise needed to develop scientifically sound epidemiologic studies.

Analyze and maintain knowledge of drug use trends by practitioners of medicine.

- Analyze data on drug use trends through a contract with IMS America.
- Provide linkages of these data to adverse drug reaction data for comparative drug risk assessments.

Disseminate and utilize drug and biological experience information to help reduce adverse experiences.

- Systematically supply timely and significant new drug experience information to the appropriate drug review division to assist its continuing reevaluation of drug labeling.
- Respond to requests for drug experience information by physicians, hospitals, and other segments of the medical community.
- Collaborate with other FDA units in developing and implementing mechanisms for communicating information to and from consumers and health professionals on proper drug selection and use.
- Act as a data resource to the staff of the FDA Drug Bulletin to assist them in keeping the nation's practitioners informed on all important new drug and biological product experience findings; and publish a monthly series of current drug experience literature alerts reviewed by FDA in the American Journal of Hospital Pharmacy.

Analyze poisoning case report data received from Poison Control Centers and other sources of epidemiological data to evaluate risk, identify acute toxic hazards, and evaluate trends in poisoning.

- Assess and evaluate appropriate data on the consequences of non-medical drug use.
- Review overdose labeling of all prescription and selected OTC drugs and veterinary drug products.
- Provide evaluation of requests for exemptions from the Poison Prevention Packaging Act to the Consumer Product Safety Commission.
- Compile and disseminate a Poison Control Center Directory; respond to information requests.
- Assist the Poison Prevention Week Council in national poison prevention activities.

Project Interaction:

New Drug Evaluation: The NDE project utilizes information developed by the DETA project for its continuous reevaluation of approved NDAs and initial evaluation of new INDs and NDAs. Also, DETA provides data needed in the determination of recommendations for production of Drug Enforcement Agency (DEA) scheduled drugs.

Bioresearch Monitoring: Drugs and Biologics: The DETA project collects and computerizes information on methadone adverse drug reactions to help identify possible abuse or significant adverse reactions.

Prescription Drug Advertising and Labeling: The DETA project reviews the adverse reaction section of labels for appropriate drugs, and actively participates in the class labeling project. The DETA project also reviews the overdose sections of labeling.

Drug Quality Assurance: The DETA project exchanges information on reports of mutual interest relating to adverse effects associated with defects in drugs.

Other Federal Agencies

Consumer Product Safety Commission (CPSC): Data on injuries from ingestion of household products are made available to the Commissioner of CPSC, and are the key factors in regulatory priorities under the Poison Prevention Packaging Act.

Environmental Protection Agency (EPA): Case report data are made available to EPA for use in determining the prevalence and hazards of misusing products covered under the Federal Insecticide, Fungicide, and Rodenticide Act.

National Center for Health Statistics (NCHS): Work with NCHS on the development and use of data bases suitable for the assessment of drug and biologic experience.

Centers for Disease Control (CDC): Collaborate with the CDC on projects of mutual interest.

Responsible Contact:

Charles Anello, Sc.D. - Center for Drugs and Biologics

Other Contacts:

**B. Chism - ORA
K. Giles - CPSC
P. Preuss - CPSC
R. Gross - EPA**

Drug Quality Assurance

Project Abstract:

FDA is responsible for monitoring the overall quality of drugs and maintaining drug establishment registration and drug product listing. It must also ensure that the manufacturing, processing, packing, and holding of drugs, and the facilities and controls used in these processes, are such that the highest quality products feasible will be marketed.

Without proper process validation and control, marketed drugs may be deficient in many ways, such as being sub- or superpotent, contaminated with other drugs, compounded with the wrong active ingredient, and/or contaminated with microorganisms. To protect the public, FDA seeks to prevent these deficiencies by monitoring the quality of all drugs marketed in the U.S. through process inspections and sample analyses. FDA supports this effort by improving drug analytical methodology and developing processing standards. FDA also strives to achieve voluntary support from the pharmaceutical industry whenever possible, informing firms of problems with their products or manufacturing processes so that correction may be accomplished as expeditiously as possible.

Congress has provided for the certification of insulin on a batch-by-batch basis prior to distribution. FDA tests, assays, and evaluates samples of all batches of insulin manufactured for sale in this country.

FDA also maintains lists of all registered drug establishments and all human drugs commercially marketed in the U.S. This mandatory registration and listing makes available to FDA information essential for effective regulation of the U.S. drug marketplace. In addition to providing information on drug establishments, the listing enables the Agency to uniquely identify each drug by means of the drug listing number (National Drug Code).

Project Mission:

Assure that human drugs marketed in the U.S. meet established standards by monitoring drug manufacturing processes and product quality and by identifying and removing from the marketplace those drugs not produced in compliance with the requirements of current Good Manufacturing Practice (GMP) regulations or not meeting established test specifications. Develop the necessary processing standards and guidance to ensure that drug products being marketed are of the highest quality possible. Certify all insulin batches prior to marketing. Maintain establishment registration and product listing files.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and pertinent sections of 21 CFR.

Applicable Sections: Chapters II, III, V, VII, and VIII of the FD&C Act, and in particular: Section 501, which states that drugs shall be considered adulterated if they contain any foreign substance or are not manufactured properly; Section 502, which establishes labeling requirements; Section 506, which mandates FDA certification of all batches of insulin prior to marketing; and Section 510, which pertains to required establishment registration, required listing of drugs and devices, and required biennial inspection of all registered establishments.

Project Activities:

Monitor the quality of all drugs marketed in the United States.

- Inspect domestic and foreign drug firms to prevent defective drugs from being produced by determining the adequacy of current manufacturing practices to produce consistently high quality drugs for commercial sale as well as for purchase by federal agencies.
- Operate a voluntary drug product reporting system to enable FDA to identify industry-wide problems which otherwise could not be detected.
- Conduct a national drug quality testing program with samples analyzed at both the Center for Drugs and Biologics and field laboratories.
- Evaluate and assay all batches of insulin submitted by manufacturers for certification.
- Analyze samples collected as part of field district surveillance programs.
- Remove from the market those drugs not meeting specifications by applying recall procedures or necessary legal sanctions, including seizures, prosecutions, and injunctions.
- Attempt to obtain voluntary industry compliance with regulations, and apply appropriate legal sanctions as needed.
- Meet the statutory obligation of Section 510(h) which requires inspection of each registered drug firm every two years.
- Conduct research on chemical and biological analytical procedures, instrumentation development, and adaptation to drug monitoring.

Maintain and develop standards for product manufacturing improvements, and participate in industry-sponsored conferences and provide guidance to the regulated industry.

- Develop and update, as appropriate, regulations and guidelines for drug manufacturing and control.
- Confer with domestic and foreign industry representatives and government regulatory representatives, to keep abreast of and encourage improvement in current state-of-the-art drug manufacturing and quality control technology.
- Participate in industry conferences, workshops, and seminars to promote voluntary compliance with the FD&C Act and regulations.

Register regulated establishments, and maintain a current listing of all registered establishments engaged in the manufacture, preparation, compounding, or propagation of drug products.

Maintain a current listing of all drugs marketed in the U. S. including their composition and labeling.

- Maintain a computerized data bank describing drug products marketed in the U. S. whether manufactured domestically or imported.
- Publish the National Drug Code Directory which serves as a reference for all public and private organizations buying prescription drugs.

Project Interaction:

DQA's drug listing activity provides data on listed products and registered establishments for most Human Drugs Program projects.

New Drug Evaluation: Manufacturing standards and product specifications established in approved NDAs are enforced by DQA activities.

Generic Drug Standards: The GDS project recommends improved official standards to the United States Pharmacopeia (USP). Enforcement of improved official standards is the responsibility of the DQA project.

Biopharmaceutics: The BIO project establishes testing procedures and standards applicable to laboratory tests of bioavailability and is used by DQA in regulatory actions.

Over-the-Counter Drug Evaluation: The OTC project supplies scientific data and information to the DQA project for any necessary regulatory follow up on those OTC products not covered under OTC Drug Final Monographs.

Drug Experience and Trends Analysis: The DETA project provides data on injuries due to drug ingestion, to support necessary compliance activities.

Other Federal Agencies

Department of Defense; Drug Enforcement Administration; General Services Administration; Federal Emergency Management Agency; Health Resources and Services Administration; Veterans Administration; Occupational Safety and Health Administration; Health Care Financing Administration; and Environmental Protection Agency: The establishment inspections, product testing, and drug listing activity of DQA provides information to these agencies.

Securities and Exchange Commission (SEC): DQA provides information as requested.

Responsible Contact:

Daniel L. Michels - Center for Drugs and Biologics

Other Contacts:

F. Desmond - CDB
B. Chism - ORA

Generic Drug Standards

Project Abstract:

All drug products marketed in the U. S. are required to meet established standards of strength, quality, and purity. These drug standards are specified in either approved New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs) or official compendia. Through its conduct of drug application reviews and continuing evaluation of the official compendia, FDA participates in establishing and improving the standards. FDA also has the responsibility of monitoring the drug products for compliance with the standards.

The law designates the United States Pharmacopeia (USP), the Homeopathic Pharmacopeia of the United States, and the National Formulary as official compendia. The standards specified in these compendia become public standards which are widely utilized throughout the drug industry as basic criteria for drug product quality.

Historically, the Agency relied upon the NDA process to establish single product standards. This approach was assumed adequate because, in most situations, multisource distribution of the drug was not a consideration. As a result, participation in the process of establishing public standards was usually limited to situations where specific standards were needed for the Agency's regulatory purposes or were matters of personal interest to individual scientists within the FDA.

The nation has experienced significant increases in the costs of health care delivery. Although drug costs are not a primary contributor to these increased costs, government attention has recently centered on possible reductions in costs as a result of federal programs allowing substitution of generics for brand name drug products. Many states have also embraced the substitution concept by repealing long-standing legal restrictions against generics. The drug substitution issue immediately prompted concerns about the relative quality and equivalence of generic drug products. Both the medical community and the public found cause to question whether products with prices significantly lower than brand name products were, in fact, equivalent and interchangeable. To assure that the quality of generic drugs was satisfactory, the Agency initiated appropriate action. A result has been the subsequent recognition of the increased importance of public standards for generics and the crucial role of the official compendia.

Project Mission:

Contribute to the development and evaluation of public standards for human drug products as published in official compendia.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Sections 201, 501, 502, and 707 of the Act define drugs, compendia, compendial requirements for drugs, and provide for Agency participation in the revision of USP and in the development of methods of analysis and mechanical and physical tests necessary to meet its needs.

Project Activities:

Maintain liaison between the FDA and USP to coordinate and resolve all specific compendial standard issues.

- Act as the officially designated representative for all human drug activities involving USP.
- Coordinate all initiatives and responses concerning compendial drug standards proposed for incorporation in the USP.

Plan, implement, and manage a public standard development program to revise, evaluate or develop proposed compendial monographs and methodology.

- Carry out an evaluation program to identify needed compendial monographs or revisions to existing monographs.
- Develop and propose revisions to existing compendial monographs and propose new monographs.
- Review and validate proposed compendial procedures and methodology to determine their adequacy to serve as regulatory methods for multisource drugs.

Project Interaction:

Biopharmaceutics: The Biopharmaceutics project reviews dissolution methods and specifications, and coordinates publication of regulations on bioequivalence.

Bioresearch Monitoring: Drugs and Biologics: The Bioresearch Monitoring project provides advice on monographs.

Generic Drug Evaluation: The Generic Drug Evaluation project identifies marketed generic drugs.

Drug Experience and Trends Analysis: The DETA project identifies drug use trends used to assign priorities for standard/monograph development.

Drug Quality Assurance: The DQA project provides data on surveys, results from the Drug Product Problem Reporting System, and Drug Listing and Registration data. It also implements compliance programs to assure the adequacy of marketed drugs in meeting existing standards.

New Drug Evaluation: The NDE project provides analytical and formulation data on new drugs.

Over-the-Counter Drug Evaluation: The OTC project reviews the compendial issues for OTC drugs (e.g., OTC monographs).

Prescription Drug Advertising and Labeling: This project provides review of labeling for compendial drugs.

Responsible Contact:

Charma A. Konnor - Center for Drugs and Biologics

Other Contacts:

B. Chism - ORA
Meade North - CDB

New Drug Evaluation

Project Abstract:

The first federal legislation dealing with standards of quality in foods and drugs was the Pure Foods and Drugs Act of 1906 which required that drugs not be adulterated or misbranded. The Food, Drug, and Cosmetic Act (FD&C Act) of 1938 extended Federal authority related to the regulation of "new drugs" by establishing a requirement that a manufacturer submit to FDA evidence demonstrating the safety of a new drug in the form of a New Drug Application (NDA) and secure FDA approval before introducing a drug product into the market. Federal authority was further strengthened by passage of the Kefauver-Harris Amendment of 1962 which added the requirement that substantial evidence from well controlled clinical investigations demonstrating the effectiveness of new drugs also be submitted and approved by FDA prior to marketing. The 1962 amendment provided for other safeguards intended to protect research subjects receiving a new drug during its period of clinical investigation.

Sponsors of investigations of new drugs or new uses of approved drugs must file a Notice of Claimed Investigational Exemption for a New Drug (IND) before beginning human experimentation. The IND must contain data on the results of animal testing, the proposed protocol for human clinical testing, the structural formula of the drug, and other data required by the Act. In addition to evaluating such IND submissions, FDA monitors the conduct of ongoing clinical investigations to assure their compliance with the applicable FDA regulations. Changes in design or implementation of an ongoing study must also be reported to FDA.

An NDA must contain: (1) full reports of investigations, including clinical investigations, that demonstrate the drug is safe and effective; (2) a full statement of the drug's composition; (3) a full description of the methods used in, and the facilities and controls used for, the manufacturing, processing, and packing of the drug; (4) samples of the drug and components as may be required; and (5) specimens of the proposed labeling. FDA publishes a summary describing the basis for its decision to approve an NDA.

NDA holders who wish to make changes in the conditions described in their approved NDA may have to submit a supplemental NDA and secure FDA approval, before implementing the changes. In addition, an NDA holder is required to submit periodic reports to FDA describing reports of adverse reactions that have come to their attention, published and unpublished medical literature, and marketing data on the drug. The NDA holder must also notify FDA immediately of any serious adverse reactions that are reported to them.

FDA develops regulations and guidelines which seek to assist drug sponsors and investigators in efficiently developing high quality evidence required for FDA's review. FDA also responds to requests for information from consumers, industry, Congress, and other government agencies. One specific aspect of FDA's safety and efficacy review involves an assessment of the potential addictive liability or potential for abuse of a new drug. These concerns are carefully evaluated prior to approval of the drug, and appropriate precautions are recommended. FDA advises the Drug Enforcement Administration (DEA) on how specific new drugs should be controlled under the special schedules of the Controlled Substances Act. FDA also provides DEA with estimates of the medical and scientific need for drugs falling under Schedule II for DEA's use in determination of production quotas. FDA also cooperates with the National Institute on Drug Abuse (NIDA) in the development of new approaches to the treatment of drug dependence.

Project Mission:

Assure that: (1) drugs approved for marketing have demonstrated adequate evidence of safety and effectiveness; (2) drugs are properly labeled; (3) once marketed, experience in use confirms this judgment; (4) clinical investigations of new drugs are properly designed and adequately safeguard the rights of human subjects while developing high quality data on safety and effectiveness; and (5) the chemical composition, means of manufacture, and various standards and methods assure that manufactured products are of high quality.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 201(p) defines a new drug; Section 301(d) prohibits any person from introducing or delivering for introduction into interstate commerce any new drug unless it is the subject of an approved NDA as required by Section 505. FDA is also authorized to exercise strict control over the use of investigational drugs undergoing clinical trials.

Project Activities:

Evaluate the safety and efficacy of new drugs.

- Evaluate INDs, IND Amendments, and reports on the progress of drug investigations.
- Evaluate original NDAs and NDA supplements.
- Evaluate proposed methods of manufacture, standards and methods, and chemical composition.
- Conduct pre-approval inspections of the manufacturing processes for compliance with current Good Manufacturing Practices.
- Evaluate periodic reports of adverse reactions and medical literature on marketed drugs.
- Obtain advice on safety and efficacy issues from consultants, experts, and therapeutic drug class advisory committees.
- Meet with sponsors of INDs and NDAs regarding drug development and evaluation activities.
- Classify INDs and NDAs by chemical and therapeutic significance, and report on the status of drugs which are new molecular entities, and new combinations, or important therapeutic gains.
- Assure adequate documentation of the history and results of the decision making process associated with the review and approval of various NDA submissions.

Develop new guidelines, regulations, and labeling.

- Develop revised regulations applicable to new drug evaluation activities.
- Assure that labeling for approved new drugs complies with new labeling guidelines.
- Disseminate clinical guidelines for development of new drugs by sponsors and investigators.
- Develop guidelines for industry's use in drafting various NDA submissions.
- Assure currency of review guidelines used by medical officers, pharmacologists, chemists, microbiologists, and biostatisticians in their work.

Respond to requests for information and improve the management of the new drug evaluation process.

- Respond to Freedom of Information requests and other requests for information, from Congress, consumers, and others.
- Implement improvements in management and scientific information systems and paperwork management.
- Seek to devise means for simplifying the submission demands for pre- and post-approval applications.

Evaluate the abuse potential of investigational drugs, new drugs, and marketed drugs, and make recommendations for appropriate action.

- Determine scientific and medical needs for Schedule I and II controlled drugs, and provide recommendations to DEA for production quotas.
- Cooperate with the NIDA in the development of new drug treatments for opiate dependence.
- Recommend drugs for control under the Controlled Substances Act to DEA.
- Review and evaluate INDs and NDAs for evidence of drug abuse potential, and recommend appropriate action.

Conduct research which supports new drug evaluation.

- Develop, through intramural research, in vitro and in vivo models for evaluating certain toxicological effects of drugs, models for determining the specific short- and long-term effects of selected drugs, and other improvements in drug evaluation methodologies.

Participate in the international community of drug regulatory organizations.

- Participate in, share information with, and seek to assist foreign drug regulatory organizations.

Project Interaction:

Bioresearch Monitoring: Drugs and Biologics: This project provides for monitoring the compliance of preclinical and clinical investigations with the existing standards that seek to assure protection of human subjects and influence production of high quality data. The project also initiates investigations on both a surveillance and "for cause" basis.

Biopharmaceutics: The BIO project reviews proposed studies and resulting bioavailability data submitted in NDAs and provides advice on any problems relating to biopharmaceutics.

Drug Experience and Trends Analysis: The DETA project provides adverse drug information to the reviewers of drug applications for their use in assessing the risk associated with new drugs once they are in widespread use. It also provides data on trends in the use of drugs which can be utilized in concluding the appropriateness of levels of use, the potential for drug abuse, and alternatives for corrective action when needed. It also provides data to support FDA's recommendations to the DEA for control schedules of drugs with great hazard potential.

Drug Quality Assurance: The DQA project utilizes information and medical expertise provided by NDE for establishing priorities and selecting drugs for quality assurance studies.

Prescription Drug Advertising and Labeling: This project reviews labeling material for new drugs and utilizes the medical and scientific expertise provided by NDE to evaluate advertising claims. Class labeling for related drugs and patient labeling for particular prescription drugs are developed. The project also coordinates the re-labeling of approved NDA drugs in accordance with labeling guidelines.

Generic Drug Evaluation: This project utilizes the information and medical and scientific expertise provided by NDE for evaluating DESI drugs and Abbreviated New Drug Applications.

Over-the-Counter Drug Evaluation: The OTC project utilizes the information and medical and scientific expertise provided by NDE to evaluate both marketed OTC drugs, and OTC drugs in the IND and NDA phases.

Responsible Contacts:

Madge L. Crouch - Center for Drugs and Biologics
Richard A. Terselic - Center for Drugs and Biologics

Other Contacts:

B. Chism - ORA

Over-the-Counter Drug Evaluation

Project Abstract:

Provisions for evaluation of new drugs were first introduced as part of the Food, Drug, and Cosmetic Act (FD&C Act). These provisions required that a manufacturer submit a New Drug Application (NDA) to prove safety to FDA for approval before a drug could be marketed. In 1962, Congress passed the Kefauver-Harris Bill, amending the Act to require that all new drugs, including over-the-counter (OTC) drugs, be approved for effectiveness as well as for safety before marketing.

Beginning in 1966, FDA contracted with the National Academy of Sciences/National Research Council for an efficacy review of approximately 4,000 prescription and 512 OTC drugs approved between 1938 and 1962 for safety only. Over 300 of the OTC drugs were found to be ineffective for one or more of their intended uses, justifying a total review of the OTC drug market. It was determined that Drug Efficacy Study Implementation (DESI) Final Orders would cover 78 of these products, but the other 434 should be deferred for the upcoming OTC drug review. In 1972, FDA announced the inauguration of its Drug Evaluation Project, in its continuing effort to assure that every drug currently on the market is safe and effective for its intended uses.

The Agency, through rulemaking procedures, will establish standards for approximately 72 therapeutic categories of OTC drugs through publication of Final Monographs or regulations in the Federal Register. Marketed OTC drugs will be required to comply with these monographs, which will include acceptable active ingredients (combinations, when appropriate), dosage ranges, indications for use, and labeling.

In 1973, Supreme Court opinions on four DESI court cases impacted on the OTC Drug Review through the Court's affirming FDA's authority to promulgate regulations in the absence of express authority in the FD&C Act; and concluding that rulemaking procedures may properly be directed to classes or groups rather than requiring litigation on a case-by-case, product-by-product basis.

Under the method of classifying OTC drugs by categories, 17 Advisory Review Panels of nongovernment, qualified experts were convened to review 27 designated categories of drugs (which have since been increased to approximately 72).

The review panels evaluated the information received from drug firms and all other interested persons to determine the safety and efficacy of OTC drug products and the adequacy of their labeling. Each panel advised the Agency on the conditions under which OTC drugs in each specific category can be marketed and, therefore, are generally

recognized as safe, effective, and not misbranded. All of the panel reports have been published in the Federal Register. The Agency reviews the conclusions and recommendations of each panel and the comments received from interested persons. FDA has published Tentative Final and Final Monographs for some drug categories and is developing Tentative Final and Final Monographs for the other drug categories.

As final regulations are published, compliance programs will be issued to and implemented by the field to ensure that drugs failing to comply with the regulations are removed from the market.

Project Mission:

Develop standards for the safety and efficacy of all OTC drugs, and monitor implementation of these standards to assure that all OTC drug products are properly formulated and labeled and that drugs which fail to comply with the standards are removed from the market.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Sections 301, 502, 505, and 701 authorize FDA to remove drugs from the market if there is adulteration, misbranding, or a lack of evidence supporting safety and/or efficacy for the conditions of use identified in the labeling.

Project Activities:

Monograph development--Prepare and publish in the Federal Register Tentative Final Monographs and Final Monographs or regulations for all OTC drug categories.

- Coordinate any issues regarding policy decisions with FDA's OTC Drug Steering Committee.
- Evaluate clinical protocols and resultant data to substantiate claims for all OTC drugs placed in Category III (i.e., those products for which research must be conducted and study data submitted to FDA before final safe and effective classifications can be made).
- Reclassify Category III drugs as Category I (Safe and Effective for Claims) or Category II (Not Safe and Effective for Claims) as evaluated and published in the Federal Register.

Monograph implementation--Conduct follow-up activities related to the publication of Final Monographs or regulations, or Special Notices in the Federal Register.

- Screen and review all OTC drug submissions (petitions for exemptions or amendments, NDA applications for deviation from monographs), and evaluate data for appropriate action.
- Modify or update Final Monographs as needed, e.g., when new scientific data justify an update of these regulations.

Surveillance/compliance activities--Pursuant to the publication of OTC Drug Final Monographs or regulations, issue and monitor compliance programs.

- Identify those products affected by each Final Monograph or regulation.
- Develop and issue follow-up compliance programs to the field to cover the Final Monographs or regulations as they are published.
- Initiate surveillance efforts through inspections and sampling by the field upon effective dates of each Final Monograph or regulation to ensure that OTC drugs which fail to comply with the Final Monographs or regulations are removed from the market.

Informational and educational activities--Provide consumer and professional informational and educational programs.

- Give formal presentations to professional and consumer groups (e.g., speeches, lectures, and seminars related to the OTC Drug Evaluation project).
- Participate in Agency-sponsored OTC drug consumer education programs (e.g., Consumer Affairs Officers' programs).
- Provide data and information pursuant to Freedom of Information regulations (e.g., panel minutes, panel reports, data submissions, etc).
- Respond to professional and consumer inquiries.

Project Interaction:

Drug Quality Assurance: The DQA project may provide data to identify OTC drug products that meet or fail to comply with the OTC Drug Final Monographs. This project also assists with any regulatory activities.

New Drug Evaluation: The NDE project provides medical and scientific information needed to evaluate both marketed OTC drugs and OTC drugs in the IND and NDA phases.

Drug Experience and Trends Analysis: The DETA project provides support to OTC drug compliance activities by providing information pertinent to injuries caused by OTC drugs.

Prescription Drug Advertising and Labeling: The Prescription Drug Advertising and Labeling project provides or receives labeling guidance on products that represent overlap between prescription drugs and OTC drugs, as well as sharing experiences gained in consumer education with reference to labeling for patients.

Responsible Contact:

William E. Gilbertson, Pharm. D. - Center for Drugs and Biologics

Other Contacts:

G. Rachanow - CDB
R. Apodaca - CDB
B. Chism - ORA

Bacterial and Allergenic Products

Project Abstract:

Bacterial products include antigens, toxoids, vaccines, bacterial antitoxins, and bacterial test reagents such as tuberculin. Allergenic products are products which are intended to diagnose or to hyposensitize individuals allergic to various substances.

FDA licenses bacterial products and allergenics prior to their marketing, and monitors these products while on the market to assure that they conform to safety and efficacy requirements. FDA monitors published literature and conferences concerned with discussion and research for these products. FDA conducts research to devise methods of measurement of safety, potency and stability of products, as well as research directed at understanding mechanisms of pathogenesis and disease prevention.

Project Mission:

Assure the safety and efficacy of bacterial and allergenic products and related products.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and PHS Act.

Applicable Sections: Section 351 of the PHS Act authorizes FDA to license biological products and manufacturing establishments. Chapter V of the FD&C Act states that drugs must be safe and effective, and authorizes FDA to regulate bacterial and allergenic products and establishments.

Project Activities:

License bacterial products and allergenic extracts prior to marketing and monitor these products to assure that they conform to safety and efficacy requirements.

- Review production, laboratory, and clinical data submitted to support license applications, as well as information concerning investigational new drugs (IND biologics).
- Review protocols on licensed products and test samples prior to release for potency and safety. (Licensed products are subject to lot testing by FDA before each lot is marketed.)

- Conduct inspections of establishments producing licensed bacterial vaccines and allergenic products to assure that they are continuing to follow safe manufacturing protocols and testing procedures specified in support of their license applications.

Conduct research to improve product testing, safety, and efficacy.

- Continue research on in vitro and in vivo characterization of allergenic products. This includes clinical and immunological studies.
- Continue studies on polysaccharide antigens, including studies of structure and immune responses. Continue studies of products combining polysaccharide and protein antigens.
- Continue studies directed toward understanding the pathogenesis of bacterial diseases, including studies on the genetic control of virulence factors, mechanism of action of bacterial toxins and the immunity to selected toxoids.
- Expand the use of monoclonal antibodies in studying bacterial and allergenic products.
- Continue studies directed toward the development of more specific skin and serologic tests for use in the diagnosis of tuberculosis and related mycobacterial infections.
- Continue research on procedures for evaluating mycoplasma contamination of cell substrates and the development of procedures which may be used to evaluate the pathogenesis of mycoplasma disease and its prevention.
- Continue studies directed at understanding the host-parasite relationship in pertussis; evaluate candidate antigens; develop tests for determination of potency, immunogenicity, and freedom from toxicity.

Project Interaction:

Bioresearch Monitoring: Drugs and Biologics: The Bioresearch Monitoring project assures the quality and integrity of bioresearch data submitted to this project.

Drug Experience and Trends Analysis: Conducts post-marketing surveillance of drugs and biologics.

Responsible Contact:

M. Carolyn Hardegree, M.D. - Center for Drugs and Biologics

Other Contact:

C. Cross - ORA

Blood and Blood Products

Project Abstract:

Blood and blood products include whole blood, plasma, platelets, red blood cells, antihemophilic factor, factor IX, plasma protein fraction, albumin, and immune globulins. These products, often used to treat life-threatening illness or injury, may cause adverse reactions and infectious disease in some patients. Diagnostic reagents, used to determine the compatibility of recipients and blood products and to exclude units that might transmit infectious disease, are also studied and regulated.

Prior to July 1972, blood and blood products were regulated by the Division of Biologics Standards (DBS), National Institutes of Health. DBS had authority to register and license approximately 6,000 intrastate blood establishments which were not subject to federal regulation. In 1972, DBS was transferred to FDA. FDA initiated and completed a program during that year to register all unlicensed blood banking and transfusion establishments. In 1974, FDA extended its authority by requiring the licensure of all establishments engaged in the manufacture or preparation of source plasma (human).

FDA reviews premarketing license applications for blood establishments and blood products. FDA monitors both licensed and registered blood establishments and licensed products to ensure that good manufacturing practices are followed. The Agency also develops methodology and conducts tests to ensure that blood and blood products are safe.

Project Mission:

Assure that blood, blood products and devices associated with their manufacture and use are safe, effective, and adequately labeled.

Applicable Legal Authority:

Applicable Statutes: PHS Act; FD&C Act, as amended by the Medical Device Amendments of 1976.

Applicable Sections: Section 351 of the PHS Act authorizes FDA to license blood products and blood processing establishments. Chapter V of the FD&C Act states that drugs (blood) must be safe and effective, and authorizes FDA to regulate drug products and establishments. The 1976 Device Amendments as they apply to diagnostic reagents are implemented for those reagents which are also biologics.

Project Activities:

Review premarketing license applications for blood establishments and blood products.

- Review and evaluate establishment license applications.
- Review INDs.
- Review and evaluate blood product license applications and test the products for purity, potency, safety and efficacy.

Monitor both licensed and unlicensed establishments to ensure that good manufacturing practices are followed.

- Conduct inspections of manufacturers and processors of human blood and blood products.
- Analyze data from the experience reporting system for human blood and blood products to detect adverse reactions which could indicate product deficiencies.
- Conduct the Blood Compliance Program including the retrieval and analysis of compliance data obtained from blood bank registration.

Develop methodology and conduct tests to ensure that blood and blood products are safe.

- Develop and implement improved policies and procedures for monitoring clinical investigations of blood products in humans, and for reviewing product and establishment license applications.
- Continue studies on the preparation of platelets and leukocyte products; red blood cell preservation; and potency and stability of immune globulin antihemophilic factor and other blood products including factor IX, urokinase, and streptokinase. (These studies are needed to determine the safe storage conditions and stability of these products.)
- Review manufacturers' protocols and test samples of individual lots of blood products and diagnostic products to determine if the manufacturing procedures specified in the license application to support product safety are being continued.
- Continue the investigation of hepatitis to reduce the transmission of infection through whole blood and plasma products, and evaluation of the impact on product safety of required "third generation" tests of blood and blood products for hepatitis antigens.

- Conduct a research program in the immunology of transplantation antigens.
- Search for enzymic and proenzymic contaminants of immune globulin products and evaluate their potential effects on stability, safety, and/or efficacy.
- Analyze molecular characteristics and behavior of albumin and albumin-containing products as affected by heating and other processing steps.
- Evaluate safety and efficacy of current and potential tests for HTLV-III virus.
- Study donors found to have positive HTLV-III antibody screening tests.
- Conduct research on the relationship of human leukemia viruses to the safety of blood and blood products.
- Approve containers for the collection, storage, and shipment of blood and plasma.
- Conduct research into modification of the immune response by biologicals, particularly regarding their effects on lipid metabolism.
- Investigate parameters related to the safety of injectable monoclonal antibodies. Analyze the B-cell immune response to defined antigens.

Project Interaction:

Bioresearch Monitoring: Drugs and Biologics: The Bioresearch Monitoring project assures the quality and integrity of bioresearch data submitted to this project.

Responsible Contact:

John C. Petricciani, M.D. - Center for Drugs and Biologics

Other Contact:

C. Cross - ORA

Viral and Rickettsial Products

Project Abstract:

This project meets FDA's responsibility to assure the safety, potency, and efficacy of biologics useful in the prevention of viral and rickettsial diseases. These include live vaccines such as measles, rubella, mumps, smallpox, polio, adenovirus, and yellow fever; killed vaccines such as influenza, rabies, hepatitis B virus, and typhus. Also included are experimental live or inactivated vaccines and viruses such as varicella, cytomegalovirus, herpes simplex, retrovirus vaccines, and hepatitis A and B viruses. Virus-specific immune globulins and lymphokines such as interferon and interleukin 2 are also included.

Project Mission:

Assure that viral and rickettsial products are safe, effective, and adequately labeled.

Applicable Legal Authority:

Applicable Statutes: PHS Act and FD&C Act.

Applicable Sections: Section 351 of the PHS Act authorizes FDA to license biological products and manufacturing establishments. Chapter V of the FD&C Act states that drugs must be safe and effective and authorizes FDA to regulate both drugs (viral and rickettsial products) and establishments.

Project Activities:

License viral and rickettsial products to assure that they conform to safety and efficacy requirements.

- Review all production, laboratory, and clinical data submitted in support of license applications and information concerning investigational new drugs (IND biologics).
- Review protocols on licensed products and test samples prior to release for safety and potency. (Licensed products are subject to batch testing by FDA before each batch is marketed.)
- Monitor procedures used by manufacturers in the transport and distribution of products.

- Conduct inspections of all establishments producing viral and rickettsial vaccines to assure that they are continuing to follow the manufacturing and test procedures specified in their license applications.
- Perform clinical studies to evaluate the safety and efficacy of viral and rickettsial biologics.
- Prepare additional standards for certain vaccines already in use in order to assure a firm regulatory basis for enforcement.

Conduct research to improve product testing, safety, and efficacy.

- Evaluate potency test information on poliovirus, influenza, rabies, yellow fever vaccines, interferon and interleukin 2, correlating these data with vaccine and lymphokine effectiveness.
- Develop programs for evaluating hybridoma, recombinant DNA, and synthetic vaccine technologies.
- Develop more meaningful criteria for evaluating the safety of oral poliovirus vaccines by an extensive review of all monkey neurovirulence tests performed with vaccines produced since 1961.
- Develop better test procedures for the detection of extraneous and possibly latent agents or oncogenic (tumor-producing) viruses as contaminants of viral and rickettsial vaccines and other biologics. Specific emphasis is placed on the AIDS virus.
- Continue surveillance of possible long-term adverse effects of immunization against viral and rickettsial diseases.
- Continue basic and applied research programs to generate information needed for appropriate evaluation of potential safety, efficacy, mechanisms of action, purity potency and other significant characteristics of experimental biologicals, including retroviruses, herpes viruses, lymphokines, and others.

Project Interaction:

Bioresearch Monitoring: Drugs and Biologics: The Bioresearch Monitoring project assures the quality and integrity of bioresearch data submitted to this project.

Responsible Contact:

Gerald V. Quinnan, Jr., M.D. - Center for Drugs and Biologics

Other Contact:

C. Cross - ORA

Health Fraud: Human Drugs and Biologics

Project Abstract:

FDA has established the Health Fraud Project to focus the Agency's activities in combating the deceptive and misleading promotion of regulated products. Health fraud products are defined as generally harmless and ineffective products to which people with serious disease conditions may turn instead of seeking or continuing proper medical treatment, or harmless and worthless articles promoted to improve general health, well-being, or appearance.

The Health Fraud program within the Center for Drugs and Biologics includes the surveillance, investigation, and regulatory action as necessary of drugs and biologicals identified as presenting consumers with indirect health hazards and major economic fraud. Once detected, health fraud products are carefully selected for regulatory attention within the competing priorities of the Agency. In contrast, drugs and biologicals which threaten direct health hazards are given immediate attention by FDA.

Fraudulent products are marketed under a variety of circumstances. Some are distributed by sincere but misguided individuals, others are promotional schemes by "quick-buck artists" and swindlers. Some representative examples of health fraud products are sobriety aids, herpes remedies, oriental herbals, anabolic steroids, and miscellaneous enzymes.

Project Mission:

To detect major health fraud products and operations and to initiate appropriate measures to achieve correction and prevent future or continuing violations. To educate consumers through publicity before their health or pocketbooks are adversely affected.

Applicable Legal Authority:

Applicable Statutes: FD&C Act and PHS Act.

Applicable Sections: Sections 201, 301, 502, and 705 of the FD&C Act and section 351 of the PMS Act define drugs and biologicals and authorize FDA to seize, prosecute and enjoin or otherwise prevent marketing of products because of the lack of evidence supporting safety and/or efficacy for the conditions of use identified in the labeling.

Project Activities:

- Direct the investigation of drugs and biologicals with unwarranted claims which may represent indirect health hazards or present a major economic fraud.
- Formulate strategy for dealing effectively with health fraud products as individual cases are identified through surveillance activities.
- Initiate corrective measures including removal of health fraud products from the market and preventing continuing violations.
- Issue public advisories and/or warnings, if necessary, to caution consumers who may be potentially victimized by such products.

Project Interaction:

New Drug Evaluation; Bacterial and Allergenic Products; Blood and Blood Products; Viral and Rickettsial Products: These projects provide scientific and medical support to dispute claims made for health fraud products.

Over-the-Counter Drug Evaluation: This project provides information on claims for OTC products not permissible under the OTC Drug Evaluation Project.

Drug Quality Assurance: This project performs laboratory testing support and furnishes information from drug product defect reporting systems, drug listing, and establishment registration files.

Drug Experience and Trends Analysis: This project provides information about adverse effects on consumers to support compliance activities.

Other Federal Agencies

U.S. Postal Service; Federal Trade Commission; Securities and Exchange Commission: These agencies conduct health fraud investigations either jointly with FDA or by themselves under statutes administered separately by them.

Responsible Contact:

Rudolf Apodaca - Center for Drugs and Biologics

Other Contacts:

B. Chism - ORA

ANIMAL DRUGS AND FEEDS

Program Abstract:

Veterinary drugs are used to treat or prevent diseases in animals and to improve production of food-producing animals. FDA is responsible for reviewing all New Animal Drug Applications (NADAs) within specified time limits to ensure that the drugs are safe and effective for animals and that food from these animals is safe before the drugs are approved for marketing. The Agency maintains continuing surveillance over all animal drugs, devices, and feeds marketed in interstate commerce to ensure their compliance with the FD&C Act.

Significant efforts are being directed toward the expansion of research programs to provide better science for the regulation of animal drugs having a human health impact.

FDA regulates safe and proper use of drugs in animal feeds. Because of the large number of facilities subject to inspection, FDA approaches the medicated feed area through a federal/state partnership for more efficient utilization of FDA's limited resources.

An Emergency Response Program in the animal feeds and feed ingredients drug areas provides a multidisciplinary emergency response capability, available on an on-call basis, to assist in the investigation of animal and animal feed contamination incidents or subsequent contamination of human foods of animal origin.

FDA's Center for Veterinary Medicine (CVM) is a participant in FDA's Small Business Program initiative. There are many small businesses in the medicated feed and animal health industries that have had infrequent or no prior contact with FDA. Such firms are invited to meet with FDA representatives to discuss the nature of their obligations to the consumer under the FD&C Act.

Environmental impact consideration is an integral part of the Agency's regulatory process. The assessment of environmental factors includes the identification of the environment that may be affected by a proposed action; the evaluation of pertinent environmental data; and the consideration of alternatives consistent with drug safety and effectiveness, and human safety.

Surveillance of marketed products and responsible agribusiness industry is accomplished through review of drug experience reports and compliance programs implemented by the FDA field offices through inspections, sample collections and analysis, investigations, and other activities. Regulatory actions are taken as needed to control violative goods and firms.

Program Mission:

Assure that only safe and effective animal drugs, devices, feeds, and food additives are marketed; and assure that foods from animals that are administered drugs and food additives, in accordance with label directions, are safe for human consumption.

Applicable Legal Authority:

Applicable Statutes: FD&C Act; National Environmental Protection Act; Fair Packaging and Labeling Act; and Drug Listing Act.

Applicable Sections: FD&C Act: Sections 201, 402, 403, 406, 409, 501, 502, 510, 512, 704, and 801; under authority delegated to the Director as in 21 CFR, Part 5.

Program Activities:

- Review "Notice of Claimed Investigational Exemption for a New Animal Drug" (INAD) and NADAs to ensure that drugs will be safe and effective for animals and that no harmful drug residues will occur in food derived from animals.
- Monitor the veterinary drug production industry by inspecting plant facilities and collecting and testing drug samples. Approve regulatory actions, when indicated, and monitor recalls.
- Survey feed and feed ingredients, review and approve medicated feed applications, inspect feed mills, and conduct industry information programs to ensure that animal feeds are not adulterated. Conduct inspections of medicated feed mills in a cooperative federal/state program. Regulatory action is taken when indicated.
- Monitor nonclinical laboratories to ensure they are in compliance with the Agency's Good Laboratory Practice (GLP) regulations.
- Monitor clinical investigators and investigational drug sponsors to evaluate the accuracy of their bioresearch data.
- Develop, test, and evaluate rapid screening methodologies that can be used by the U. S. Department of Agriculture (USDA) for surveillance of drug residues and by FDA for supporting regulatory activities.
- Conduct regulatory research related to tissue residues and toxic compounds in animal feeds.

- Approve new animal drugs and food additives prior to their marketing.
- Maintain surveillance of marketed animal drugs and devices; review Drug Experience Reports.
- Conduct consumer education programs.

Responsible Contact:

Lester M. Crawford, D.V.M., Ph.D. - Director, Center for Veterinary
Medicine

1. The first part of the report is devoted to a general description of the project and its objectives.

2. The second part of the report describes the methodology used in the study, including the selection of subjects, the design of the experiment, and the procedures for data collection and analysis.

3. The third part of the report presents the results of the study, including the data collected and the statistical analysis performed.

4. The fourth part of the report discusses the implications of the findings and provides conclusions and recommendations for future research.

5. The fifth part of the report is a summary of the entire study.

6. The sixth part of the report is a list of references, including books, articles, and other sources used in the study.

7. The seventh part of the report is a list of appendices, including tables, figures, and other supplementary material.

8. The eighth part of the report is a list of acknowledgments, thanking those who provided assistance and support during the study.

9. The ninth part of the report is a list of abbreviations and a glossary of terms used in the study.

10. The tenth part of the report is a list of footnotes, providing additional information and references.

11. The eleventh part of the report is a list of tables, providing a summary of the data collected.

12. The twelfth part of the report is a list of figures, providing a visual representation of the data.

PROGRAM RESOURCE SUMMARYAnimal Drugs and Feeds¹

Project Title
Animal Drugs: Bioresearch Monitoring
Safety of Animal Derived Human Foods
New Animal Drug Evaluation
Animal Feed Safety
Monitoring Marketed Animal Drugs & Devices
Voluntary Compliance in Animal Drugs & Feeds
TOTALS

FY 86 RESOURCES			
Totals		Percent of \$(000)	
FTE	\$ (000)	Program	FDA
20	\$ 1,023	4.3%	0.2%
98	5,694	23.9	1.4
92	5,452	22.9	1.3
138	7,713	32.5	1.9
66	3,389	14.3	0.8
9	501	2.1	0.1
423	\$23,772	100%	5.7%

FIELD/HQ DISTRIBUTION OF 1986 RESOURCES			
FTE		\$ (000)	
FIELD	HQ	FIELD	HQ
8	12	\$ 339	\$ 684
7	91	292	5,402
27	65	1,134	4,318
94	45	5,078	2,635
24	42	1,007	2,382
0	9	0	501
160	263	\$7,850	\$15,922

¹Resources reflect FDA FY 86 President's Budget.

Animal Drugs: Bioresearch Monitoring

Project Abstract:

In evaluating the safety and effectiveness of new animal drugs and food additives, FDA must rely on data obtained by clinical and non-clinical investigators selected by the sponsors to conduct studies on the drugs in question. Effectively conducted trials are essential to proper decisionmaking on the safety and efficacy of new animal drugs. Incompetently conducted trials and the submission of false data confound judgments of safety and effectiveness, and place those subjects exposed to new animal drugs at unnecessary risk. Therefore, in addition to reviewing data submitted to the sponsor, it is necessary that FDA be assured that the data are properly and reliably obtained.

The premature marketing of a number of inadequately tested animal drugs was one of the factors that led to the passage of the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act (FD&C Act). These Amendments and the 1963 Investigational Drug Regulations provided FDA with the authority to exercise a much closer control over the clinical testing of investigational drugs. Therefore, FDA promulgates and updates regulations and guidelines to make policy clear and consistent; monitors and evaluates drug research through surveillance/compliance programs; and develops educational programs that explicitly communicate guidance to the research community.

Recent events and controversy have called into question the adequacy of data received by FDA for making critical determinations regarding the approval of drugs and food additives. The fundamental objective of the program is to ensure that research data submitted to the Agency are truthful and adequate for determining whether the drugs and food additives should be or should continue to be marketed in interstate commerce. The Bioresearch Monitoring program within the Center for Veterinary Medicine (CVM) includes surveillance and follow-up inspections of nonclinical laboratories, clinical investigators, and sponsors/monitors of investigational new animal drugs.

Project Mission:

Assure that clinical and nonclinical investigations are conducted in a scientific manner that will demonstrate the safety and effectiveness of animal drugs to the target species and safety to the ultimate consumer of food and food additives in products of animal origin.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 409 requires that petitions for food additives, including those intended for animal food, must contain full reports of investigations that show an additive is safe for use, and that a food additive petition cannot be approved until safety to both the target animal and to consumers of food products of animal origin is assured. Section 512 states that new animal drug applications must contain a full report of investigations that demonstrate whether a drug is safe and effective for use, and that an application cannot be approved until safety and effectiveness are assured. An approved application may be withdrawn under Section 512(e) if new evidence subsequently shows a drug not to be safe or effective or if an application contains an untrue statement. Section 704 provides investigational authority.

Project Activities:

Monitor nonclinical laboratories to determine that they are in compliance with the Agency's Good Laboratory Practices regulations.

- Provide surveillance coverage of all laboratories known to be engaging in safety tests on animal drugs and food additives.
- Evaluate research data from nonclinical laboratories as to completeness and accuracy for use in making safety decisions concerning animal drug and food additive products.
- Audit key studies to ensure the scientific validity of the bases of new animal drug and food additive approvals.
- Inform and advise violative firms as to corrective measures required.

Monitor clinical investigators and animal drug sponsors to determine the accuracy of their bioresearch data.

- Inspect clinical investigators and drug sponsors for drug accountability, data validity, reporting accuracy, and protocol adherence.
- Verify that investigational drugs and treated animals remain within the conditions of their authorized use parameters.
- Examine inspection reports to detect emergent problems, serious adverse reactions, or other unanticipated phenomena.

- Evaluate proposed and existing investigational regulations in order to provide the most effective input to the pending final regulations for both clinical investigators and sponsors/monitors of investigational drugs.

Implement existing nonclinical and clinical regulations.

- Initiate appropriate compliance actions for violations under the final GLP regulations.
- Continue to enforce existing clinical regulations and to inform investigators, monitors, and sponsors of the requirements of the proposed regulations.

Provide Freedom of Information services in response to requests.

Project Interaction:

Medical and Radiological Device Product Evaluation; Medical and Radiological Device Monitoring and Quality Conformance; Bioresearch Monitoring: Human Drugs and Biologics; Food Additives: These projects and the Animal Drugs: Bioresearch Monitoring project are part of the Agency-wide bioresearch monitoring activities.

Animal Feed Safety; Monitoring Marketed Animal Drugs and Devices; New Animal Drug Evaluation; Safety of Animal-Derived Human Foods: The Animal Drugs: Bioresearch Monitoring project assures the acceptability of the animal drug bioresearch data submitted to the Agency on CVM-regulated products.

Responsible Contact:

Norman R. Tufts, V.M.D. - Center for Veterinary Medicine

Other Contacts:

D. Pocurull -CVM
D. Baker - CVM
E. Brisson - ORA

Safety of Animal-Derived Human Foods

Project Abstract:

Animal drugs are used in food producing animals to improve production and to treat and control disease. Many of these drugs have the potential for leaving drug residues in edible animal tissues that may be hazardous for humans.

New Animal Drug Applications (NADAs), Investigational New Animal Drug (INAD) Exemption Notices, and Food Additive Petitions (FAPs) for use in food animals must contain information to show that meat, milk, and eggs derived from animals receiving the drug or food additive are safe to humans, and that an acceptable method of analysis is available to monitor products in the food chain for unsafe residues. FDA reviews and evaluates these data for adequacy before approving the drugs and food additives or permitting use of experimental animals or their products for food.

USDA monitors edible animal tissues for residues of drugs, pesticides, and environmental contaminants. FDA has established tolerances for drug residues in tissues of the animals for which the drug was approved, based on data and information required in the NADA. Tolerances or action levels have been set by FDA or the Environmental Protection Agency (EPA) for other chemicals in foods derived from animals.

FDA investigates violative (over tolerance) residues and can take regulatory action against the person or firm responsible for causing the adulteration. Information gained from these investigations, residue data, specific residue problems, and other sources, may raise safety questions requiring Agency action, such as requests for additional data on a drug, NADA withdrawal, change of tolerance level, or product recall.

Project Mission:

Assure that foods derived from animals contain no unsafe drug residue or other chemical adulterant and that harmful residues do not enter the human food supply.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 512 requires that new animal drugs not be marketed without an approved NADA. Among other things, the NADA must contain data showing safety to humans consuming edible products from animals receiving the drug. Similar requirements for food additives are specified in Section 409. Section 512 also authorizes FDA to withdraw approval of an NADA if the drug is not shown to be safe or is found to be unsafe to man or to the animal for which the drug is intended. This section also states that no residues of certain drugs will be found in any edible portion of such animals after slaughter or in any food yielded by or derived from animals. Section 402 specifies what constitutes adulteration of food under the Act. Section 406 requires that the Secretary of HHS promulgate regulations limiting the quantity of any poisonous or deleterious substance which is required to be added to food or which cannot be avoided.

Project Activities:

INADs.

- Review INADs for food animal drugs and food additives to assure safety of food from animals going to slaughter that have been administered investigational drugs, and from milk and eggs.

NADAs and FAPs.

- Review the human food safety portions of NADAs and FAPs to assure food safety.
- Provide a focal point for intra- and interagency activities concerning food safety of animal drugs and animal-use food additives.
- Develop, implement, and evaluate intra- and extramural research programs to assist in answering questions concerning the food safety of animal drugs and food additives, and to furnish information necessary to implement regulatory programs.

Assessment of public health significance of drug and food additive residues.

- Conduct research to determine the toxicological significance of drug and food additive residues in food of animal origin.
- Conduct review of food safety aspects of marketed animal drugs when questions arise as to adequacy of safety data supporting approval.

- Recommend withdrawal or need for additional data on marketed drugs, depending on information available on the food safety of the product.

Surveillance of drug, pesticide, and other chemical residues in edible animal tissue.

- Develop, test, and evaluate residue methodology for surveillance and regulatory purposes.
- Maintain liaison with CVM/USDA to assist in the coordination of the project including residue monitoring, problem areas, and regulatory actions.
- Assist in regulatory actions against firms and/or individuals responsible for causing illegal drug and other chemical residues in edible animal tissues.

Evaluation of residue information.

- Evaluate information relating to human food safety, including residue data, concerning industry and nonindustry experience with the drug product after its approval.

Informational/educational aspects of the project.

- Develop educational and informational materials that serve as guides for producers and growers of animals for food.
- Respond to inquiries from industry, Congress, consumers, the press, and professional organizations regarding the human food safety aspects of residue issues and promulgate advisory opinions.

Provide Freedom of Information services in response to requests.

Project Interaction:

Animal Feed Safety: Both the Safety of Animal-Derived Human Foods and Animal Feed Safety projects are concerned with drugs or other chemicals in feeds that may lead to harmful residues in food for man. Unsafe tissue residues identified in the CVM human-food safety project may be due to problems in medicated feed mixing (lack of Good Manufacturing Practices) or other causes.

Animal Drugs: Bioresearch Monitoring: Monitoring of nonclinical research studies and laboratories to determine compliance with Good Laboratory Practices regulations provides a valuable source of information to food safety evaluation of new animal drugs and food additives. Information from these inspections that concern studies related to food safety are evaluated by human food safety personnel.

Monitoring Marketed Animal Drugs and Devices: Ongoing surveillance of marketed drugs includes the assurance that food from animals receiving the drug is safe for human consumption. A "for cause" review of animal drugs for adequacy of food safety information involves close cooperation between the marketed drug project and the human food safety project.

New Animal Drug Evaluation: Human food safety aspects of NADAs, INADs, and FAPs are reviewed and evaluated under the Safety of Animal-Derived Human Foods project. The New Animal Drug Evaluation project personnel consolidate all aspects of the application and petition to declare overall adequacy of the application or petition.

CVM Emergency Response Program: An emergency response team provides a multidisciplinary emergency response capability, available on an on-call basis, to assist in the investigation of animal and animal feed contamination incidents or subsequent contamination of human food of animal origin.

National Center for Toxicological Research (NCTR): NCTR conducts research for CVM in areas concerned with human food safety. The Safety of Animal-Derived Human Foods project uses these data to assist in regulatory functions associated with drugs or food additives.

Other Federal Agencies

U.S. Department of Agriculture (USDA): The USDA has primary responsibility for monitoring the meat supply for drug and chemical residues. When residues are found, the human food safety project interacts by assessing the risk of such residues and recommending corrective action.

Responsible Contact:

J. Settepani, Ph.D. - Center for Veterinary Medicine

Other Contacts:

Marvin A. Norcross, V.M.D., Ph.D. - CVM
M. Strong - ORA

New Animal Drug Evaluation

Project Abstract:

Drugs are administered to animals for the treatment, control and/or prevention of disease, and for improving animal production. Drugs that are unsafe and ineffective may result in serious economic losses to animal producers as well as injury to or loss of valued pets and show animals. Improperly compounded or labeled, or otherwise unsafe, drugs may cause hazardous residues in human food when such drugs are utilized in food-producing animals.

In 1938, Congress amended the Food, Drug and Cosmetic Act (FD&C Act) to require that new drugs should be reviewed prior to approval for marketing, to ensure their safety. In 1962, Congress further directed that new drugs should also be reviewed for effectiveness before approval.

Applicants must submit notices to FDA before they begin clinical investigations of drugs in animals. The information must contain investigational labeling, a description of the drug, a record of the quantities of drugs shipped, the names of investigators, and, in the case of drugs used in food animals, data to demonstrate the safety of food derived from animals used in new drug investigations.

Applicants must submit a New Animal Drug Application (NADA) and obtain approval prior to marketing new animal drugs. NADAs contain safety and effectiveness data for animals and safety data for edible products if the drug is to be administered to food-producing animals. Applications may also contain data to insure safety to the environment from the reduction and use of the drug.

Researchers have found evidence that the low level use of antibacterial drugs in animal feeds may cause a buildup in numbers of antibacterial-resistant microorganisms in humans. As a result, FDA now requires that antibacterials for long-term low level use in animal feed must be proven, using a new battery of tests, to not significantly contribute to resistance in animals and humans.

Project Mission:

Assure that new animal drugs are safe and effective, and compounded, formulated and manufactured properly.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 501 states that drugs must be produced under Good Manufacturing Practices (GMPs) to assure their safety, identity, quality, purity, and strength. Section 510 states that the establishments that produce such drugs must be registered with FDA. Section 512 states that new animal drugs may not be marketed without an approved NADA. It further states that the NADA must contain information listing the composition of the drug, description of methods, facilities and controls used for manufacturing, as well as data on the safety and effectiveness of such drugs. FDA is authorized to remove from the market any drug that is not safe and/or effective following due process procedures.

Project Activities:

Authorize the use of animal drugs for investigational purposes to ensure that drugs will be safe for animals and humans consuming edible products.

- Review Investigational New Animal Drug (INAD) Exemptions in conjunction with the Safety of Animal-Derived Human Foods project for adequacy of food safety data, drug withdrawal periods, and labeling.
- Review "Expedited Review" INADs according to NADA standards on a priority basis.
- Develop guidelines for sponsors of new animal drugs and food additives.
- Issue letters of acknowledgment to sponsors commenting on the conduct of specific experimental studies detailed under protocols submitted with an INAD exemption.

Review NADAs for safety and effectiveness.

- Review NADAs, in conjunction with the Safety of Animal-Derived Human Foods project, for effectiveness, animal safety, environmental impact, manufacturing, chemistry, stability, labeling, and human food safety.
- Develop, implement, and evaluate intra- and extramural research programs to assist in answering questions concerning the safety and effectiveness of animal drugs and food additives and to furnish information necessary to implement regulatory programs.

Provide Freedom of Information services in response to requests.

Project Interaction:

Animal Drugs: Bioresearch Monitoring: The bioresearch monitoring project ensures the quality and integrity of bioresearch data submitted to this project and also conducts inspections in the field and evaluates results of bioresearch data.

Safety of Animal-Derived Human Foods: The human foods safety project integrates the validations of analytical methodology between FDA laboratories and USDA.

Monitoring Marketed Animal Drugs and Devices: The Monitoring Marketing Animal Drugs and Devices project evaluates information in drug experience reports.

Voluntary Compliance in Animal Drugs and Feeds: Efforts will be made to increase industry understanding of the data requirements necessary for new animal drug approval.

Other Federal Agencies

Drug Enforcement Administration (DEA): DEA and FDA have a joint responsibility for regulation of controlled substances in new animal drugs.

Environmental Protection Agency (EPA): EPA and FDA have a joint responsibility for regulation of the use of pesticides as drugs.

U. S. Department of Agriculture (USDA): USDA and FDA have a joint responsibility for food animal drug residue method validation and special projects.

Department of the Interior (DOI): DOI and FDA have a joint responsibility for use of drugs for aquaculture and wildlife.

Responsible Contact:

R. Carnevale, V.M.D. - Center for Veterinary Medicine

Other Contacts:

Marvin A. Norcross, V.M.D., Ph.D. - CVM
C. Andres - ORA
M. Strong - ORA

Animal Feed Safety

Project Abstract:

Animal feeds, including food for companion animals, may contain adulterants such as pesticides and heavy metals, naturally occurring toxicants, or pathogenic microorganisms and industrial chemicals, that would render the feed unsafe for consumption. The two primary concerns are the health hazard to the animal for which the feed is intended and the public health hazard if unsafe residues from the adulterant occur in the food products originating from these animals.

Animal feeds are permitted to contain drugs if the drugs have been evaluated for safety and effectiveness and approved by the Agency. Improper manufacturing practices of these medicated feeds can result in excessive drug levels or drug adulteration of feeds that may cause over-tolerance drug residues in meat or other animal products marketed for human consumption.

FDA samples feeds and feed ingredients to ensure that they are not adulterated or misbranded. In addition, FDA reviews and approves medicated feed applications to ensure the accuracy of formulation and labeling in accordance with published regulations. Applicants must file Food Additive Petitions (FAPs) and/or a food additive regulation must be in effect prior to marketing animal food additives. FAPs contain animal safety and physical or technical effects data, and safety data for humans if the food additive is administered to food-producing animals. FDA also provides regulatory inspectional coverage of the feed industry and educational activities for the agribusiness community.

Project Mission:

Assure that animal foods are not adulterated or misbranded. In addition, assure that all medicated feeds are properly formulated, manufactured, labeled, and distributed so that they are safe and effective for their intended use in animals, and that harmful residues do not enter the human food supply.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Sections 402 and 403 state that animal foods must be free from adulterants that may be injurious to health, and that such foods must be properly labeled in accordance with the Act. Section 406 focuses upon poisonous and deleterious substances. These sections apply to foods for both companion and food-producing animals. Section 512 states that medicated feeds must be safe and effective for their intended uses. Sections 501 and 502 require that medicated animal feeds be properly manufactured, packaged, and labeled. FDA is authorized to approve and/or revoke the use of such feeds if they do not conform to the regulations. Section 704 provides investigational authority. Section 409 states that the safety of food additives must be demonstrated prior to approval and issuance of a food additive regulation.

Project Activities:

Conduct surveillance of feeds and feed ingredients to identify any that are adulterated or misbranded.

- Sample and analyze animal feeds and feed ingredients to ensure that they are free of adulterants. Regulatory action is taken when indicated.

Review and approve medicated feed applications, Generally Recognized As Safe (GRAS) applications and FAPs.

- Review all medicated feed applications for formulation accuracy, adequacy of manufacturing practices and labels, and adherence to approved regulations.
- Review GRAS affirmation and FAPs for product description, history of use, analytical detection procedures, functionality data, and data on safety to humans and animals.

Provide regulatory coverage of industry.

- Inspect medicated feed manufacturing sites either by FDA field staff or through the cooperative federal/state inspection program. (The federal/state program provides for the states to inspect medicated feed manufacturing operations and to report violations to FDA and/or initiate appropriate state follow-up).
- Collect and analyze feed samples through the cooperative federal/state program.
- Collect and analyze samples of feed ingredients for toxic substance contamination where there is suspected potential for danger to animal and/or public health.

- Initiate regulatory action (e.g., seizure, injunction, or prosecution) against firms or individuals responsible for causing the manufacture of illegal medicated feeds or the interstate movement of otherwise adulterated or misbranded animal feeds and feed ingredients.

- Initiate and/or review recalls and evaluate animal health hazards.

Develop background information concerning toxic and pathogenic effects of the adulterants upon the population at risk and render advisory opinions on specific cases.

- Review literature to establish an information base relating to specific adulterants.
- Render advisory opinions on health hazards related to feed/food contamination incidents for support of regulatory actions.
- Develop and evaluate compliance programs to direct the field offices and assist in the monitoring of marketed feeds and feed ingredients.
- Develop, implement, and evaluate intra- and extramural research programs to furnish essential information necessary to implement regulatory programs.

Provide informational and educational services relating to animal feed safety.

- Create an awareness of the requirements of the FD&C Act and the critical need for preventing chemical contamination of animal feeds, through dissemination of information/education materials to the agribusiness community.
- Respond to inquiries from consumers, Congress, industry, the press, and professional organizations regarding the safety of animal feeds and products derived from food animals.
- Provide Freedom of Information services in response to requests.

Project Interaction:

Safety of Animal-Derived Human Foods: Both the Animal Feed Safety project and the Safety of Animal-Derived Human Foods project are directed toward assuring the harmful drug residues and chemical adulterants in edible animal tissues are prevented from entering the human food chain. The Animal Feed Safety project focuses on whether feed processing operations have adequate controls to assure there are no errors in production that would result in contamination.

Animal Drugs: Bioresearch Monitoring: The Animal Drugs: Bioresearch Monitoring project ensures the quality and integrity of bioresearch data submitted to this project.

Voluntary Compliance in Animal Drugs and Feeds: The voluntary compliance project increases compliance with the FD&C Act through educational workshops and programs.

Chemical Contaminants: The purpose of this project is to ensure that humans are protected against undue risk from industrial chemicals, pesticides, toxic metals, natural toxins, and radionuclide contaminants in the food supply. Surveillance and research activities are coordinated with the Animal Feed Safety project.

Responsible Contact:

George Graber, Ph.D. - Center for Veterinary Medicine

Other Contacts:

W. Price, Ph.D. - CVM

E. Ballitch - CVM

M. Strong - ORA

Monitoring Marketed Animal Drugs and Devices

Project Abstract:

The Food, Drug and Cosmetic (FD&C) Act directs FDA to maintain constant surveillance of all drugs and devices marketed in interstate commerce. Among these are thousands of products labeled for use in animals to treat or prevent disease or to improve production.

To accomplish this goal, the Agency is mandated to inspect every animal drug manufacturing facility at least once every two years. The facilities, manufacturing procedures, formulations, and labeling relating to marketed products are reviewed to determine their compliance with the Act and current Agency regulations.

When violations are detected, they are brought to the attention of the involved firm for voluntary correction. Failure to correct violations within a reasonable period as determined by reinspection and sample analysis will result in regulatory action being taken in the form of seizure of the violative goods or injunction of the firm and/or prosecution of the responsible individuals. Seizure may occur without reinspection.

The nature of the regulatory action will depend, in part, on the seriousness of the violation. Violations may result in products that are directly hazardous to animals due to their methods of manufacture or formulation or directions for use. Additionally, products may constitute a hazard to humans either from their direct misuse or abuse or indirectly through the presence of unsafe residues in the tissues of food-producing animals. Numerous products are associated with economic fraud because their labeling or promotional materials claim that they are effective when they have not been proven to be so.

The Act requires that all animal drugs that are not generally recognized as safe and effective be approved by the Agency prior to marketing on the basis of studies performed by the sponsor. Any animal drug marketed in interstate commerce that is not generally recognized as safe and effective and that is not approved as safe and effective by the Agency is subject to regulatory action.

Additionally, even animal drugs that are approved by the Agency may become misbranded or adulterated due to their method of distribution or use. For some products, adequate directions for safe and effective use by laypersons cannot be written and the products must be used only by or on the order of a veterinarian. When such products are sold

directly to laypersons without the legitimate order of a veterinarian, they become misbranded and they and the persons causing the violation are subject to regulatory action. Use of approved products in an unapproved manner may cause such products to be adulterated under the FD&C Act and they and the persons causing the violation may be subject to regulatory action.

Following new animal drug approval, the sponsor is required to maintain complete records and submit complete reports on the approved products. These records and reports include all information relating to the safety and effectiveness of approved products that come to the attention of the firm, through voluntary submission by its customers, literature searches, or studies conducted by or reported to the firm. All such information must be submitted to the Agency within time frames provided by regulation. The information serves as a basis for determining whether there are grounds for modifying manufacturing procedures, formulation, or labeling to assure a safe and effective product, or for withdrawing approval of the drug and removing it from the market.

Project Mission:

Assure that animal drugs and devices marketed in interstate commerce are safe and effective and are not otherwise adulterated or misbranded.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Sections 201 (g), 201 (h), 201 (w), 409, 501, 502, 510, 512, 704 and 801.

Project Activities:

Drug experience reporting.

- Evaluate all information submitted in Drug Experience Reports, required for approved new animal drugs under 21 CFR 510.300 and .301, and initiate appropriate action to insure that such products are safe and effective or are removed from the market.

Animal drug labeling.

- Review advertising, promotional material, and labeling of animal drugs and devices in interstate commerce.

Adverse drug reaction reporting.

- Review Adverse Reaction Reports from all sources, including Consumer Injury Reports.
- Initiate and monitor contracts for the reporting of adverse reactions to veterinary drugs.

NADAs.

- Initiate, review, and recommend appropriate action on regulatory supplements to approved NADAs.
- Initiate the causal review of approved NADAs based on adverse information received in Drug Experience Reports or otherwise.
- Withdraw approval of new animal drug applications and provide technical and administrative resources during resultant hearings when necessary.

Educational and informational services.

- Develop and disseminate educational and informational materials to industry and the consumer.
- Promote voluntary compliance by the industry generally, and by individual firms.
- Provide Freedom of Information services in response to requests.
- Develop and issue advisory opinions, responses to congressional inquiries, consumers, and industry correspondence.

Regulatory coverage of domestic drugs and devices.

- Develop, implement, and evaluate intra- and extramural research programs to furnish essential information necessary to carry out regulatory programs.
- Initiate and/or review letters of adverse findings and regulatory letters.
- Initiate and/or review regulatory actions involving legal measures, such as seizure, prosecution, and injunction, to correct violative conditions.
- Initiate, review, and monitor recalls and evaluate animal health hazards.
- Inspect manufacturing and distribution facilities to insure compliance with NADA requirements, GMPs, etc., and/or to determine compliance with all other existing sections of the FD&C Act and with regulations.

- Initiate and/or review Establishment Inspections.
- Collect and analyze samples of marketed animal drugs to determine their compliance with the FD&C Act, and remove from the market those that fail to comply.
- Develop and evaluate compliance programs to direct the field offices and assist in the monitoring of marketed drugs and devices.

Regulatory coverage of imported drugs and devices.

- Inspect, sample, and analyze imported drugs and devices to insure compliance with the FD&C Act.
- Monitor imports and refuse entry to violative products.

Illegal distribution and extralabel use.

- Investigate reports of illegal distribution of veterinary prescription drugs.
- Curtail extralabel use of veterinary drugs through educational activities or direct investigations of potentially hazardous misuse.

Project Interaction:

New Animal Drug Evaluation: The New Animal Drug Evaluation project assures that animal drugs and food additives used in animals are safe and effective.

Safety of Animal-Derived Human Foods: The Safety of Animal-Derived Human Foods project assures that foods derived from animals contain no unsafe drug residue or other harmful, chemical adulterant.

Animal Drugs: Bioresearch Monitoring: The Bioresearch Monitoring project ensures the quality and integrity of bioresearch data submitted to this project. This project involves the conduct of inspections in the field and the evaluation of results of bioresearch data.

Voluntary Compliance in Animal Drugs and Feeds: The Voluntary Compliance project increases compliance with the FD&C Act through educational workshops and programs.

Other Federal Agencies

Drug Enforcement Agency (DEA): DEA and FDA have a joint responsibility for regulation of controlled drugs.

Environmental Protection Agency (EPA): EPA and FDA have a joint responsibility for regulation of drugs and pesticides.

U. S. Department of Agriculture (USDA): USDA and FDA have a joint responsibility for regulation of animal biologics.

Occupational Safety and Health Administration (OSHA): OSHA and FDA have a joint responsibility for regulation of animal drug manufacturing facilities.

Department of Interior (DOI): DOI and FDA have a joint responsibility for regulation of drug use in wildlife.

Responsible Contact:

Andrew J. Beaulieu, D.V.M. - Center for Veterinary Medicine

Other Contacts:

Howard Meyers, D.V.M. - CVM
E. Ballitch - CVM
David Scarr, D.V.M. - CVM
M. Strong - ORA

Voluntary Compliance in Animal Drugs and Feeds

Project Abstract:

Despite the elaborate system of laws, regulations, and inspections we have instituted in this country, the safety of our food and drugs, for the most part, depends upon the voluntary cooperation of producers, processors, distributors, retailers, etc. The number of establishments required to be inspected by FDA is increasing at a rate faster than the staff and resources necessary to inspect them. The Department and FDA, therefore, are placing increased emphasis on programs designed to promote acceptance and participation by regulated producers/industries in self-inspection, quality assurance and other voluntary compliance activities.

The CVM Voluntary Compliance Program is directed primarily toward those producers/industries involved with products intended for use on or in food-producing animals intended for human consumption; however, any industry regulated by CVM may be involved.

Significant problems involving residues in animal-derived human food products, medicated feeds, illegal import or illegal distribution of prescription drugs, health fraud, etc., are usually identified as a result of the Center's routine compliance activities or through contact with other federal, state, or local regulatory agencies. Once a problem has been isolated, CVM staff, in a coordinated effort with other Agency units, develop a strategy for encouraging producer/industry cooperation and/or compliance to resolve the problem. Strategies may include, but are not limited to developing printed and audiovisual educational materials explaining the problem and how to avoid it; speaking to leaders of national organizations to educate them about the problem and incorporate their support in resolving it; organizing workshops with affected industry personnel to gather their ideas for resolving the problem; and organizing meetings with representatives of other federal/state/local regulatory agencies to develop a unified approach to resolving the problem.

Project Mission:

Increase public health protection by improving compliance with the Food, Drug, and Cosmetic Act (FD&C Act) by FDA regulated agribusiness producers/industries through education and the voluntary adoption of self inspection and other quality assurance programs.

Applicable Legal Authority:

Applicable Statutes: FD&C Act.

Applicable Sections: Sections 402, 403, 406, 409, 501, 502, 510, 512, and 801 of the FD&C Act.

Sections 402 and 403 state that animal foods must be free from adulterants that may be injurious to health and that such foods must be properly labeled in accordance with the Act. Section 406 focuses upon poisonous and deleterious substances. These sections apply to foods for both companion and food-producing animals.

Section 409 requires that food additives, including those intended for animal food, must contain full reports of investigations that show an additive is safe for use, and that a food additive petition cannot be approved until safety to both the target animal and to consumers of food products of animals is assured.

Section 501 states that drugs must be produced under good manufacturing practices to assure their safety, identity, quality, purity, and strength. Section 502 defines when a drug or device is misbranded. Section 512 requires that a new animal drug may not be marketed without an approved NADA and that an application cannot be approved until safety and effectiveness are assured.

Section 801 establishes authority for regulation of foods, drugs, and devices that are imported or exported.

Project Activities:

Promote proper use of veterinary drugs.

- Develop educational materials on proper drug use which instructors in veterinary and other colleges can incorporate into their courses.
- Meet and work with groups such as the American Academy of Veterinary Pharmacologists and Therapeutics to encourage their support for using FDA materials.
- Promote the concept of the veterinarian as a public health protector through speeches and articles in producer publications and the lay press.
- Publish a list of approved veterinary drugs.
- Publicize the distinction between prescription and over-the-counter drug status.

- Develop an information campaign to increase practicing veterinarians' awareness of the importance of reporting adverse drug reactions and identify the procedures for reporting them.
- Develop mechanisms for distributing to practicing veterinarians summaries of adverse drug reaction reports received by CVM.
- Encourage the use of the NADA number on the label of approved veterinary drugs.

Illegal residues in animal-derived human food.

- Identify Agency needs in terms of national goals and policies.
- Utilize contacts with officials of the national producer groups (National Cattlemen's Association, National Broiler Council, National Pork Producers Council, etc.)
- Conduct epidemiology study of currently available residue reports.
- Coordinate CVM's voluntary compliance plans and operations with USDA, EPA, and other federal, state, and local counterparts.
- Develop educational/informational materials for distribution to CVM regulated industry groups.
- Speak at national and regional meetings of animal producer groups on issues of current concern to the Agency.
- Conduct educational work sessions with industry representatives in order to develop resolutions to residue problems.

Contamination of animal feedstuffs.

- Address and clarify key issues of Agency concerns related to the production of animal feeds.
- Meet with leaders of the American Feed Industry Association, National Feed Ingredient Association, National Renderers Association, and other animal feed producer groups to incorporate their support in resolving key issues.
- Provide industry groups with information and educational materials that they can utilize in the development of a quality assurance program for their members.

Project Interaction:

Safety of Animal-Derived Human Foods: Tissue residues identified in the human food safety project may represent a widespread industry problem requiring modification of customary industry procedures.

Animal Feed Safety: Tissue residues identified in the animal feed safety project may be due to problems in mixing medicated feeds or other causes.

Monitoring Marketed Animal Drugs and Devices: Ongoing surveillance of marketed drugs often reveals unexpected problems with veterinary products.

Animal Drugs: Bioresearch Monitoring: Deficiencies identified during inspections may indicate widespread misunderstanding by investigators of their responsibilities under the GLP regulations.

New Animal Drug Evaluation: Workshops for industry representatives and development of educational materials on requirements for obtaining drug approval will help the efficiency of CVM's drug approval process.

Other Federal Agencies

U.S. Department of Agriculture (USDA): The USDA has primary responsibility for monitoring the meat supply for drug and chemical residues. When patterns of residues are found, the Voluntary Compliance Program will use this data to work with industry groups to assist in resolving the problems.

Responsible Contact:

Gary E. Stefan - Center for Veterinary Medicine

Other Contacts:

W. Bixler, V.M.D. - CVM

B. Sink - CVM

M. Strong - ORA

MEDICAL DEVICES AND RADIOLOGICAL HEALTH

Program Abstract:

Under the Medical Devices and Radiological Health program, FDA pursues two overall long-range goals: to ensure the safety and effectiveness of medical devices, as provided for by the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act (FD&C Act); and to eliminate unnecessary human exposure to man-made radiation from medical, occupational, and consumer products while optimizing the results of necessary exposure, as provided for by the Radiation Control for Health and Safety Act of 1968. These goals present FDA with unique regulatory challenges in view of rapidly changing technology in the device and radiological fields. FDA regulations must effectively deal with the public health issues involved while avoiding unnecessary and undesirable restraint of technological innovation.

The Agency accomplishes its long-range goals through several activities. The safety and effectiveness of medical devices is ensured by classifying each type of medical device into the appropriate category of regulatory control (Class I, devices requiring only general controls; Class II, devices requiring standards; and Class III, devices requiring premarket approval). All devices are subject to general controls such as labeling, registration, listing, good manufacturing practices, and repair/replace/refund requirements. In addition, performance standards are being developed for Class II devices, and Class III and new devices must receive FDA approval before marketing. The Agency also conducts premarket review of new devices through the premarket notification and product development protocol provisions of the Amendments, and encourages the development of useful new devices, while protecting the rights and safety of human subjects in device investigations.

The Agency fosters prudent use of radiation-emitting devices and products by: conducting epidemiological and experimental research to assess the risk from various forms and sources of radiation; developing radiation measurement instruments and methods useful in evaluating products (e.g., diagnostic and dental x-ray units, television receivers, microwave ovens, laser products, sun lamps, and ultrasound therapy units); developing performance standards; developing guidelines to prevent unnecessary radiation exposure; and implementing survey programs to determine trends in, and the current state of, the use of radiation-emitting devices and products.

In both medical devices and radiological health areas, the Agency seeks to educate consumers, industry, and health professionals to enable them to make more informed judgments and use improved techniques.

The Agency is conducting research to determine the biological effects of exposure to radiation and to develop methods to control radiation emissions; to support the issuance of performance standards for radiation-emitting products; to conduct problem definition studies in support of regulatory standards for Class II medical devices; and to support monitoring and surveillance of both medical devices and radiological health products.

Program Mission:

Assure that the American public is not exposed to unnecessary radiation; assure that medical devices intended for human use are safe, effective, and properly labeled; and assure that information on the proper use of devices and radiological products is made available to health care professionals and the public.

Applicable Legal Authority:

Applicable Statutes: FD&C Act, as amended by the Medical Device Amendments of 1976; PHS Act, as amended by the Radiation Control for Health and Safety Act; and the Patient-Consumer Radiation Health and Safety Act.

Applicable Sections: All sections of the Medical Device Amendments of 1976. Sections 301, 311, and 354 through 360 (F) of the PHS Act provide authority to protect the public health and safety from electronic product radiation. Sections 501 through 505, 507, 510 and Sections 513-521 of the FD&C Act provide authority to protect the public health from radioactive materials in drugs and medicine.

Program Activities:

General.

- Develop regulations to implement the requirements of the Medical Device Amendments.
- Collect and evaluate information on currently marketed medical devices, including adverse effects, to support the development or updating of standards, reclassification efforts, and regulatory decisionmaking; and study and evaluate emissions and conditions of exposure to electronic products and radiopharmaceuticals to establish criteria and methods that are used to support recommendations and regulations for radiation protection.

Monitoring and Quality Conformance.

- Conduct surveillance and compliance programs to ensure that radiation-emitting products and materials are safe for their intended use, and to monitor the quality of marketed medical devices.
- Conduct biennial inspections of establishments producing Class II and Class III devices.
- When necessary, monitor recalls and initiate regulatory actions such as seizures, injunctions, and prosecutions.
- Develop and implement performance standards for Class II devices.
- Monitor restricted medical device advertising and promotional labeling, and enforce any applicable labeling requirements.
- Conduct annual registration of medical device establishments. Listing of all devices commercially marketed in the U.S. is required at the initial registration of a firm. Updates of listing data are required whenever changes are made in the list of devices being marketed.
- Conduct the Government-Wide Quality Assurance Program in conjunction with other federal agencies. The program is designed to ensure that all medical devices purchased for use by federal agencies meet the requirements of the FD&C Act, when applicable, and any additional contractual specifications.

Product Evaluation.

- Classify medical devices into regulatory control categories.
- Review notifications of intent to market new or significantly modified devices [510(k) submissions] to determine whether each product is substantially equivalent to a pre-Amendment device. If the Agency determines the device is not substantially equivalent, the manufacturer may not market the product unless it submits a premarket approval application or petitions for reclassification.
- Process petitions for reclassification or initiate reclassification actions.
- Review requests for investigational device exemptions. (Investigational devices may be exempted from Sections 502, 510, 514, 515, 516, and 706 of the Act to permit the investigational use of the device.)

- Monitor testing of investigational devices through surveillance.
- Evaluate safety and effectiveness data for Class III medical devices, which require FDA approval before they may be marketed. For Class III devices marketed prior to passage of the Medical Device Amendments, FDA may call for premarket approval applications 30 months after final classification to determine safety and effectiveness. A manufacturer must either submit a PMA or withdraw its device from the market within 90 days of such a call.
- Evaluate and monitor product development protocol (PDP) submissions. (A PDP sets forth a manufacturer's plan for developing safety and effectiveness data.) Review the notice of PDP completion to declare the protocol complete and the product marketable, or to declare it incomplete.

Bioeffects Analysis, Testing and Measurement Development.

- Assess the health effects resulting from exposure to ionizing and nonionizing radiation-emitting products and materials through epidemiological and laboratory studies.
- Conduct research to develop laboratory techniques or methodologies to test medical devices for safety, effectiveness, and compliance with labeling requirements or claims.

Education and Assistance.

- Educate users of radiation equipment and materials, as well as other medical devices, to allow them to make more informed judgments and to use improved techniques that will reduce radiation exposures and patient injuries and deaths. Disseminate medical device information to industry, consumers, and health professionals.
- Provide technical and other nonfinancial assistance to small manufacturers.

Responsible Contact:

John C. Villforth - Director, Center for Devices and Radiological Health

PROGRAM RESOURCE SUMMARYMedical Devices and Radiological Health¹

Project Title	FY 86 RESOURCES				FIELD/HQ DISTRIBUTION OF 1986 RESOURCES			
	Totals		Percent of \$		FTE		\$ (000)	
	FTE	\$ (000)	Program	FDA	FIELD	HQ	FIELD	HQ
Medical and Radiological Device Monitoring and Quality Conformance	625	\$31,701	46.4%	7.7%	354	271	\$16,239	\$15,462
Medical and Radiological Device Product Evaluation	278	15,249	22.3	3.7	13	265	540	14,709
Medical and Radiological Device Bioeffects Analysis, Testing, and Measurement Development	171	11,699	17.1	2.8	31	140	1,292	10,407
Medical and Radiological Device Education and Assistance	166	9,719	14.2	2.4	32	134	1,330	8,389
TOTALS	1,240	\$68,368	100%	16.6%	430	810	\$19,401	\$48,967

¹Resources reflect FDA FY 86 President's Budget.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	-----

1. The first part of the document is a list of names and addresses of the members of the committee. The names are listed in alphabetical order, and the addresses are given in full. The list is as follows:

Mr. J. H. Smith, 123 Main Street, New York, N. Y.
 Mr. J. D. Jones, 456 Elm Street, Boston, Mass.
 Mr. W. E. Brown, 789 Oak Street, Chicago, Ill.
 Mr. R. L. Green, 101 Pine Street, Philadelphia, Pa.
 Mr. S. K. White, 202 Cedar Street, Baltimore, Md.
 Mr. T. M. Black, 303 Maple Street, Washington, D. C.
 Mr. U. N. Gray, 404 Birch Street, St. Louis, Mo.
 Mr. V. P. Hall, 505 Spruce Street, Portland, Me.
 Mr. W. Q. King, 606 Ash Street, San Francisco, Cal.
 Mr. X. R. Lee, 707 Hickory Street, Denver, Colo.
 Mr. Y. S. Clark, 808 Walnut Street, Kansas City, Mo.
 Mr. Z. T. Evans, 909 Chestnut Street, Cincinnati, O.
 Mr. A. U. Adams, 1010 Broadway, New York, N. Y.
 Mr. B. V. Baker, 1111 Madison Avenue, New York, N. Y.
 Mr. C. W. Carter, 1212 Park Avenue, New York, N. Y.
 Mr. D. X. Davis, 1313 Fifth Avenue, New York, N. Y.
 Mr. E. Y. Edwards, 1414 Sixth Avenue, New York, N. Y.
 Mr. F. Z. Fisher, 1515 Seventh Avenue, New York, N. Y.
 Mr. G. A. Gibson, 1616 Eighth Avenue, New York, N. Y.
 Mr. H. B. Hall, 1717 Ninth Avenue, New York, N. Y.
 Mr. I. C. Hill, 1818 Tenth Avenue, New York, N. Y.
 Mr. J. D. Jones, 1919 Eleventh Avenue, New York, N. Y.
 Mr. K. E. King, 2020 Twelfth Avenue, New York, N. Y.
 Mr. L. F. Lee, 2121 Thirteenth Avenue, New York, N. Y.
 Mr. M. G. Martin, 2222 Fourteenth Avenue, New York, N. Y.
 Mr. N. H. Miller, 2323 Fifteenth Avenue, New York, N. Y.
 Mr. O. I. Olson, 2424 Sixteenth Avenue, New York, N. Y.
 Mr. P. J. Parker, 2525 Seventeenth Avenue, New York, N. Y.
 Mr. Q. K. Quinn, 2626 Eighteenth Avenue, New York, N. Y.
 Mr. R. L. Reed, 2727 Nineteenth Avenue, New York, N. Y.
 Mr. S. M. Smith, 2828 Twentieth Avenue, New York, N. Y.
 Mr. T. N. Taylor, 2929 Twenty-first Avenue, New York, N. Y.
 Mr. U. O. Upton, 3030 Twenty-second Avenue, New York, N. Y.
 Mr. V. P. Vance, 3131 Twenty-third Avenue, New York, N. Y.
 Mr. W. Q. Ward, 3232 Twenty-fourth Avenue, New York, N. Y.
 Mr. X. R. Webb, 3333 Twenty-fifth Avenue, New York, N. Y.
 Mr. Y. S. Wells, 3434 Twenty-sixth Avenue, New York, N. Y.
 Mr. Z. T. Wilson, 3535 Twenty-seventh Avenue, New York, N. Y.
 Mr. A. U. Wood, 3636 Twenty-eighth Avenue, New York, N. Y.
 Mr. B. V. Wright, 3737 Twenty-ninth Avenue, New York, N. Y.
 Mr. C. W. Young, 3838 Thirtieth Avenue, New York, N. Y.
 Mr. D. X. Zachary, 3939 Thirty-first Avenue, New York, N. Y.
 Mr. E. Y. Zimmerman, 4040 Thirty-second Avenue, New York, N. Y.

Mr. J. H. Smith, 123 Main Street, New York, N. Y.
 Mr. J. D. Jones, 456 Elm Street, Boston, Mass.
 Mr. W. E. Brown, 789 Oak Street, Chicago, Ill.
 Mr. R. L. Green, 101 Pine Street, Philadelphia, Pa.
 Mr. S. K. White, 202 Cedar Street, Baltimore, Md.
 Mr. T. M. Black, 303 Maple Street, Washington, D. C.
 Mr. U. N. Gray, 404 Birch Street, St. Louis, Mo.
 Mr. V. P. Hall, 505 Spruce Street, Portland, Me.
 Mr. W. Q. King, 606 Ash Street, San Francisco, Cal.
 Mr. X. R. Lee, 707 Hickory Street, Denver, Colo.
 Mr. Y. S. Clark, 808 Walnut Street, Kansas City, Mo.
 Mr. Z. T. Evans, 909 Chestnut Street, Cincinnati, O.
 Mr. A. U. Adams, 1010 Broadway, New York, N. Y.
 Mr. B. V. Baker, 1111 Madison Avenue, New York, N. Y.
 Mr. C. W. Carter, 1212 Park Avenue, New York, N. Y.
 Mr. D. X. Davis, 1313 Fifth Avenue, New York, N. Y.
 Mr. E. Y. Edwards, 1414 Sixth Avenue, New York, N. Y.
 Mr. F. Z. Fisher, 1515 Seventh Avenue, New York, N. Y.
 Mr. G. A. Gibson, 1616 Eighth Avenue, New York, N. Y.
 Mr. H. B. Hall, 1717 Ninth Avenue, New York, N. Y.
 Mr. I. C. Hill, 1818 Tenth Avenue, New York, N. Y.
 Mr. J. D. Jones, 1919 Eleventh Avenue, New York, N. Y.
 Mr. K. E. King, 2020 Twelfth Avenue, New York, N. Y.
 Mr. L. F. Lee, 2121 Thirteenth Avenue, New York, N. Y.
 Mr. M. G. Martin, 2222 Fourteenth Avenue, New York, N. Y.
 Mr. N. H. Miller, 2323 Fifteenth Avenue, New York, N. Y.
 Mr. O. I. Olson, 2424 Sixteenth Avenue, New York, N. Y.
 Mr. P. J. Parker, 2525 Seventeenth Avenue, New York, N. Y.
 Mr. Q. K. Quinn, 2626 Eighteenth Avenue, New York, N. Y.
 Mr. R. L. Reed, 2727 Nineteenth Avenue, New York, N. Y.
 Mr. S. M. Smith, 2828 Twentieth Avenue, New York, N. Y.
 Mr. T. N. Taylor, 2929 Twenty-first Avenue, New York, N. Y.
 Mr. U. O. Upton, 3030 Twenty-second Avenue, New York, N. Y.
 Mr. V. P. Vance, 3131 Twenty-third Avenue, New York, N. Y.
 Mr. W. Q. Ward, 3232 Twenty-fourth Avenue, New York, N. Y.
 Mr. X. R. Webb, 3333 Twenty-fifth Avenue, New York, N. Y.
 Mr. Y. S. Wells, 3434 Twenty-sixth Avenue, New York, N. Y.
 Mr. Z. T. Wilson, 3535 Twenty-seventh Avenue, New York, N. Y.
 Mr. A. U. Wood, 3636 Twenty-eighth Avenue, New York, N. Y.
 Mr. B. V. Wright, 3737 Twenty-ninth Avenue, New York, N. Y.
 Mr. C. W. Young, 3838 Thirtieth Avenue, New York, N. Y.
 Mr. D. X. Zachary, 3939 Thirty-first Avenue, New York, N. Y.
 Mr. E. Y. Zimmerman, 4040 Thirty-second Avenue, New York, N. Y.

3. The third part of the document is a list of the names and addresses of the members of the committee who have been elected to the office of Treasurer. The names are listed in alphabetical order, and the addresses are given in full. The list is as follows:

Mr. J. H. Smith, 123 Main Street, New York, N. Y.
 Mr. J. D. Jones, 456 Elm Street, Boston, Mass.
 Mr. W. E. Brown, 789 Oak Street, Chicago, Ill.
 Mr. R. L. Green, 101 Pine Street, Philadelphia, Pa.
 Mr. S. K. White, 202 Cedar Street, Baltimore, Md.
 Mr. T. M. Black, 303 Maple Street, Washington, D. C.
 Mr. U. N. Gray, 404 Birch Street, St. Louis, Mo.
 Mr. V. P. Hall, 505 Spruce Street, Portland, Me.
 Mr. W. Q. King, 606 Ash Street, San Francisco, Cal.
 Mr. X. R. Lee, 707 Hickory Street, Denver, Colo.
 Mr. Y. S. Clark, 808 Walnut Street, Kansas City, Mo.
 Mr. Z. T. Evans, 909 Chestnut Street, Cincinnati, O.
 Mr. A. U. Adams, 1010 Broadway, New York, N. Y.
 Mr. B. V. Baker, 1111 Madison Avenue, New York, N. Y.
 Mr. C. W. Carter, 1212 Park Avenue, New York, N. Y.
 Mr. D. X. Davis, 1313 Fifth Avenue, New York, N. Y.
 Mr. E. Y. Edwards, 1414 Sixth Avenue, New York, N. Y.
 Mr. F. Z. Fisher, 1515 Seventh Avenue, New York, N. Y.
 Mr. G. A. Gibson, 1616 Eighth Avenue, New York, N. Y.
 Mr. H. B. Hall, 1717 Ninth Avenue, New York, N. Y.
 Mr. I. C. Hill, 1818 Tenth Avenue, New York, N. Y.
 Mr. J. D. Jones, 1919 Eleventh Avenue, New York, N. Y.
 Mr. K. E. King, 2020 Twelfth Avenue, New York, N. Y.
 Mr. L. F. Lee, 2121 Thirteenth Avenue, New York, N. Y.
 Mr. M. G. Martin, 2222 Fourteenth Avenue, New York, N. Y.
 Mr. N. H. Miller, 2323 Fifteenth Avenue, New York, N. Y.
 Mr. O. I. Olson, 2424 Sixteenth Avenue, New York, N. Y.
 Mr. P. J. Parker, 2525 Seventeenth Avenue, New York, N. Y.
 Mr. Q. K. Quinn, 2626 Eighteenth Avenue, New York, N. Y.
 Mr. R. L. Reed, 2727 Nineteenth Avenue, New York, N. Y.
 Mr. S. M. Smith, 2828 Twentieth Avenue, New York, N. Y.
 Mr. T. N. Taylor, 2929 Twenty-first Avenue, New York, N. Y.
 Mr. U. O. Upton, 3030 Twenty-second Avenue, New York, N. Y.
 Mr. V. P. Vance, 3131 Twenty-third Avenue, New York, N. Y.
 Mr. W. Q. Ward, 3232 Twenty-fourth Avenue, New York, N. Y.
 Mr. X. R. Webb, 3333 Twenty-fifth Avenue, New York, N. Y.
 Mr. Y. S. Wells, 3434 Twenty-sixth Avenue, New York, N. Y.
 Mr. Z. T. Wilson, 3535 Twenty-seventh Avenue, New York, N. Y.
 Mr. A. U. Wood, 3636 Twenty-eighth Avenue, New York, N. Y.
 Mr. B. V. Wright, 3737 Twenty-ninth Avenue, New York, N. Y.
 Mr. C. W. Young, 3838 Thirtieth Avenue, New York, N. Y.
 Mr. D. X. Zachary, 3939 Thirty-first Avenue, New York, N. Y.
 Mr. E. Y. Zimmerman, 4040 Thirty-second Avenue, New York, N. Y.

Medical and Radiological Device Monitoring and Quality Conformance

Project Abstract:

This project incorporates all headquarters and field activities associated with monitoring overall medical and radiological device quality, maintaining establishment registration and product listing systems, monitoring device experience reports, and assuring that the manufacturing, processing, packing, storage, and installation of devices is acceptable.

This requires implementing applicable provisions of the 1976 Medical Device Amendments, monitoring devices of foreign origin, and conducting biennial inspections of domestic manufacturers of Class II and Class III products.

In addition, this project includes implementation of the following sections of the Amendments: mandatory standards, custom devices, banned devices, administrative detention, adulteration, misbranding, records and reports, information requests under 513(g), notification, and repair/replace/refund of defective products; and the Regulatory Flexibility Act and/or Executive Order 12291 when applicable.

To ensure that health practitioners are provided with high quality diagnostic equipment, FDA conducts a compliance program to enforce the diagnostic x-ray performance standard. Enforcement mechanisms include factory inspection, review of periodic reports from manufacturers, and laboratory and on-site testing.

Compliance programs are also maintained to support the enforcement of the microwave oven standard and standards for therapeutic ultrasound devices, and to monitor the performance of consumer and industrial products that are capable of emitting ionizing or nonionizing radiation.

Field measurement capability and instrumentation are maintained to support research, to investigate industrial and medical light products, and to support compliance activities for the laser, sun lamp, and mercury vapor lamp standards.

FDA also ensures that manufacturers of electronic products that have no performance standards are required to repair, replace, or refund the cost of products manufactured with a radiation safety defect.

Reports of production and safety are required for radio frequency (RF) dielectric sealers, microwave heating equipment, and microwave diathermy equipment.

The Agency conducts a Government-Wide Quality Assurance Program in cooperation with the Department of Defense and Veterans Administration. This program is designed to ensure that the medical devices purchased for use by federal agencies meet the requirements of the Food, Drug, and Cosmetic Act (FD&C Act) and any additional contractual specifications.

Finally, the Agency may initiate a variety of regulatory actions (e.g., regulatory letters, citations, seizures, injunctions, and prosecutions) and monitors recalls to maintain the quality of medical and radiological devices products.

Project Mission:

Assure that medical and radiological devices are safe and effective through implementation of regulations, surveillance of firms and products, encouragement of voluntary compliance, and initiation of necessary actions.

Applicable Legal Authority:

Applicable Statutes: FD&C Act, as amended by the Medical Device Amendments of 1976; PHS Act, as amended by the Radiation Control for Health and Safety Act; and the Patient-Consumer Radiation Health and Safety Act.

Applicable Sections: All sections of the Medical Device Amendments of 1976. Sections 301, 311, and 354 through 360 (F) of the PHS Act provide authority to protect the public health and safety from electronic product radiation. Sections 501 through 505, 507, 510, and Sections 513-521 of the FD&C Act provide authority to protect the public health from radioactive materials in drugs and medicine.

Project Activities:

- Conduct compliance operations.
- Develop mandatory standards.
- Enforce standards and regulations.
- Provide field liaison; develop compliance programs; conduct inspection planning and evaluation.
- Maintain the Registration and Listing System.
- Maintain voluntary and mandatory experience reporting systems.
- Review 90-602 submissions for radiological products.
- Review labeling.

Project Interaction:

Medical and Radiological Device Product Evaluation: The devices subject to general controls requirements are determined by the classification effort. In addition, the appropriate classification panel(s) must be consulted before a device is banned.

Bioresearch Monitoring: Human Drugs and Biologics: The Center for Drugs and Biologics monitors the general controls requirements for the good manufacturing practices regulation and the biennial inspection program for biological devices.

Other Federal Agencies

Health Resources and Services Administration; Veterans Administration; Department of Defense (HRSA; VA; DOD): A memorandum of understanding between these organizations and FDA ensures all device products purchased by these organizations meet acceptable levels of safety and effectiveness.

Consumer Product Safety Commission (CPSC): An agreement between this organization and FDA provides for the sharing of data collected by CPSC through its National Electronic Injury Surveillance System.

Veterans Administration (VA): A memorandum of understanding between FDA and VA provides for the exchange of medical device experience data.

Responsible Contact:

Walter E. Gundaker - Center for Devices and Radiological Health

Other Contact:

R. McClellan - ORA

Medical and Radiological Device Product Evaluation

Project Abstract:

This project incorporates all headquarters and field activities associated with: (1) classification of devices; (2) review of premarket notification [510(k)s] and premarket approval applications (PMAs) for medical devices, including radiological devices; (3) review of requests for investigational device exemptions (IDEs) for medical devices including radiological devices; and (4) the evaluation of product development protocols (PDPs).

With the assistance of expert advisory panels, FDA is classifying medical devices marketed prior to passage of the 1976 Medical Device Amendments into one of three regulatory control categories (Classes I, II, and III) based on the potential health risk associated with the devices.

Approximately 137 types of pre-Amendment devices will be classified in the premarket approval category (Class III) because they are (1) implantable, (2) life supporting, (3) life sustaining, or (4) potentially hazardous to life and good health and, in the expert judgment of the panels, lack adequate information to develop standards governing their safety and efficacy. Section 515 of the 1976 Medical Device Amendments requires that the manufacturer provide FDA with safety and effectiveness data for Class III devices. These premarket applications are reviewed by advisory panels and the Agency to determine approvability.

Clinical investigators typically submit testing protocols to an institutional review board (IRB) for review and approval. If the IRB approves a nonsignificant risk investigation, the investigator is deemed to have an approved IDE which is subject to abbreviated regulatory requirements. Sponsors of significant risk investigations must submit an IDE application directly to FDA after the study has been reviewed and approved by an IRB. FDA has 30 days to evaluate IDE applications; the investigation may proceed unless FDA notifies the sponsor otherwise.

The Agency also reviews notifications of intent to market a device. In these notifications, manufacturers explain that they intend to market a new device or significantly modify a device currently being marketed, how that device is similar to or different from other marketed products, and how the product conforms to any standards or premarket approval requirements. The Agency investigates the accuracy of the manufacturer's notification. Those products that are

not substantially equivalent to pre-Amendment products (products marketed prior to passage of the Amendments) or to post-Amendment products that have been classified into Class I or II, are automatically put into Class III, thus requiring premarket approval. Under this project, the Agency also reviews and approves or denies petitions for reclassification, or initiates reclassifications on its own.

As an alternative to an IDE request and a PMA, manufacturers may submit a PDP describing the plans for preclinical and clinical trials, manufacturing methods and facilities, procedures for meeting applicable performance standards, and labeling. Once the PDP is approved, the sponsor must complete the testing in accordance with the approved protocol. FDA then determines if the PDP was successfully completed. If so, the product may be marketed.

Field inspections are conducted to determine if devices described in IDEs, PDPs, or PMAs will be produced in accordance with good manufacturing practices regulations. On-site monitoring of preclinical and clinical investigations will determine if human testing procedures described in the IDE, PDP, or PMA are adequate to protect human subjects and if the laboratory data used to support the submission are reliable.

Project Mission:

Assign all devices into the regulatory control category most appropriate for the potential risk and assure that all Class III devices are safe and effective for their intended use; and ensure that clinical investigations of new devices properly safeguard human subjects while developing high-quality data on safety and efficacy.

Applicable Legal Authority:

Applicable Statutes: FD&C Act, as amended by the Medical Device Amendments of 1976.

Applicable Sections: Section 510(k), 513, 514, 515, 520 (g), (h) and (i) of the Medical Device Amendments of 1976.

Project Activities:

- Review and evaluate: Premarket Notifications [510(k)s], Premarket Approval Applications (PMAs), New and Pre-Amendment Investigational Device Exemptions (IDEs), and Product Development Protocols (PDPs) for all medical devices including radiological products.
- Track and coordinate 510(k)s, PMAs and IDEs.
- Classify and reclassify devices.
- Conduct bioresearch monitoring.

Project Interaction:

Medical and Radiological Device Monitoring and Quality Conformance:

The device establishment and product registration programs in the Medical and Radiological Device Monitoring and Quality Conformance project provide information on the number of Class III pre-Amendment products for which FDA must require premarket applications. Also, good manufacturing practices regulations developed under the former Medical Device Monitoring and Quality Assurance project will be used to determine if manufacturers with pending PMAs or PDPs can acceptably produce their products.

Bioresearch Monitoring: Human Drugs and Biologics: IDEs, PMAs, and premarket notification submissions [510(k)s] for biological devices are reviewed by the Center for Drugs and Biologics.

New Drug Evaluation: Certain activities under this project support the review of radiopharmaceuticals (INDs/NDAs). Cooperative effort also exists with respect to the medical use of drugs and light as a combined therapeutic technique.

Responsible Contact:

Robert G. Britain - Center for Devices and Radiological Health

Other Contacts:

R. McClellan - ORA
M. Nissel - CDB

Medical and Radiological Device Bioeffects Analysis, Test and Measurement Development

Project Abstract:

This project incorporates all Center for Devices and Radiological Health (CDRH) applied science activities (as distinct from scientific review), such as research on the bioeffects of various types of radiation and light, and ultrasound. Also incorporated are studies of technology evaluation and optimization, and the mechanical and biotoxic properties of implantable materials. Development of measurement techniques or modalities comprises a significant portion of this project, and supports internal and external research for this project and others.

Active participation in, and support of, consensus standards activities includes both draft standards development and test/evaluation methods. Rapidly changing technology in most segments of the device and radiological product industries requires that CDRH staff operate on a state-of-the-art level for both developing and evaluating new technology.

Human experience research and risk assessment is performed using both experimental and epidemiological approaches. Existing programs for studying trends in radiographic utilization or for evaluating the safety of nuclear medicine equipment and techniques exemplify this function.

Project Mission:

Provide a sound scientific basis for the programs and policies of CDRH.

Applicable Legal Authority:

Applicable Statutes: FD&C Act, as amended by the Medical Device Amendments of 1976, and PHS Act.

Applicable Sections: All sections of the Medical Device Amendments of 1976. Sections 301, 311, and 354 through 360 (F) of the PHS Act provide authority to protect the public health and safety from electronic product radiation. Sections 501 through 505, 507, 510, and Sections 513-521 of the FD&C Act provide authority to protect the public health from radioactive materials in drugs and medicine.

Project Activities:

- Research, testing, and measurement of products, materials, and modalities.
- New technology development and evaluation.
- Human experience research and risk assessment.
- Technical and scientific support services.

Project Interaction:

Medical and Radiological Device Monitoring and Quality Conformance; Medical and Radiological Device Product Evaluation: The Medical and Radiological Device Bioeffects Analysis, Test and Measurement Development project provides applied science and research activities, the results of which may be the basis for activities in other CDRH projects.

Other Federal Agencies

Federal Emergency Management Agency; Nuclear Regulatory Commission; Environmental Protection Agency (FEMA; NRC; EPA): Through interagency agreements these agencies provide funds to partially support the FDA cooperative agreement with the Conference of Radiation Control Program Directors to "Plan and hold an annual technical meeting of the conference members and sponsors and to develop program recommendations on reduction of radiation exposure to the population and radiation workers."

National Bureau of Standards (NBS): An interagency agreement between FDA and NBS establishes a continuing effort to provide supplemental lab support for the independent evaluation of problems associated with medical devices, and to provide specialized measurements and intercomparisons of instrumentation for standardization.

Department of Energy (DOE): An interagency agreement between FDA and DOE provides for development of tables of absorbed dose for selected radioactive products in human models.

Armed Forces Institute of Pathology (AFIP): Under an interagency agreement FDA and AFIP collaborate on a pilot project intended to assess the feasibility and usefulness of establishing an explanted prosthetic heart valve study group.

National Cancer Institute (NCI): Interagency agreements between FDA and NCI provide technical support for evaluation of hyperthermia equipment, and provide support for the study of long term effects of ionizing radiation in the beagle dog.

Naval Research Laboratory (NRL): An interagency agreement between FDA and NRL provides metallurgical and fractographic analysis support for testing and assessment of medical devices.

Responsible Contact:

Kshitij Mohan, Ph.D. - Center for Devices and Radiological Health

Other Contact:

R. McClellan - ORA

Medical and Radiological Device Education and Assistance

Project Abstract:

This project is devoted to improving device use through improving information bases and information dissemination about medical and radiological devices. At a number of stages in the design, testing, manufacture, and use of medical devices, communication may be a critical factor in the ultimate safe and effective use of the device.

FDA is charged with the task of developing guidelines that advise radiation technologists and physicians on various efficacious procedures to reduce unnecessary radiation exposure and improve diagnostic image quality. FDA must also promulgate these guidelines among federal agencies providing direct health care. Updated educational materials are continually distributed to physicians, technologists, physicists, and other health care professionals and consumers through a wide variety of means, including the FDA Consumer Affairs Officers' programs, and a number of cooperative federal-state programs.

To improve diagnostic image quality and reduce unnecessary patient exposure, FDA promotes recommendations for quality assurance programs in diagnostic radiology, nuclear medicine, and radiation therapy.

A consumer training and education program informs the public and the medical community of potential hazards from light radiation sources and of the proper use of light products.

FDA also disseminates device information to the device industry, the public, and health professionals, and provides technical and other nonfinancial assistance to small manufacturers.

Project Mission:

Promote the safe and effective use of devices by providing information, as required, to all parties involved in the development, manufacture, or use of medical and radiological devices (e.g., consumers, health practitioners, and the regulated industry).

Applicable Legal Authority:

Applicable Statutes: FD&C Act, as amended by the Medical Device Amendments of 1976; PHS Act, as amended by the Radiation Control for Health and Safety Act; and the Patient-Consumer Health and Safety Act.

Applicable Sections: All sections of the Medical Device Amendments of 1976. Sections 301, 311, and 354-360 (F) of the PHS Act provide authority to protect the public health and safety from exposure to radiation from electronic products. Sections 501-505, 507, 510 and Sections 513-521 of FD&C Act provide authority to protect the public health from radioactive material in drugs and medicine. Section 311 of the PHS Act provides authority to assist the States in developing elements of uniform state programs for control of naturally occurring radioactive materials (NARM) and NARM products.

Project Activities:

- User education programs.
- Small manufacturers technical assistance, training and liaison activities.
- Liaison with consumer and professional organizations, consumer inquiry coordination.
- Cooperative federal-state education and information programs.
- Conference of Radiation Control Program Directors.

Project Interaction:

Medical and Radiological Device Monitoring and Quality Conformance; Medical and Radiological Device Product Evaluation; Medical and Radiological Device Bioeffects Analysis, Test and Measurement Development: Education, assistance, or training needs may be identified by or associated with activities of any of the Center for Devices and Radiological Health projects. In addition, the Small Manufacturers Technical Assistance Program, which is part of this project, provides assistance to device firms. One aspect of this is the establishment of small business desks in various regions to provide information and assistance to small manufacturers.

Responsible Contact:

**Joseph S. Arcarese - Center for Devices and Radiological
Health**

Other Contact:

R. McClellan - ORA

NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

Program Abstract:

The National Center for Toxicological Research (NCTR) is an inter-agency toxicological research facility primarily dedicated to the scientific programs within FDA, but also to those of common interest to other government agencies. It participates actively in the National Toxicology Program (NTP). As part of the effort to solve public health problems caused by toxic chemicals, NCTR conducts highly sophisticated research to study not only the biological effects of potentially toxic chemicals, but also the complex mechanisms that govern their toxicity. Program emphasis is on:

- The adverse health effects of long-term exposures to low levels of chemicals and their mechanism(s) of action.
- The development of improved test methods and protocols for use in predicting the various toxic effects of chemicals.
- The development of data and methods for extrapolating from effects on laboratory animals to effects on man, to enable risk assessments to be made.
- The comprehensive toxicological bioassessment of chemicals of particular importance to regulatory agencies.

Program Mission:

To advance, by means of high quality scientific inquiry, understanding of the way in which toxic chemicals produce their harmful effects, in order to develop the capability to predict, evaluate and minimize them.

Applicable Legal Authority:

Applicable Statute: FD&C Act.

Applicable Sections: Section 402, 408, 409, and 601 of the Act state that foods, cosmetics, and pesticides must not contain any amount of deleterious substances which may be detrimental to human health. The Secretary of HHS has the authority to determine the tolerance levels of such substances in commodities.

Program Activities:

Hazard Identification.

The first step in risk assessment, hazard identification, seeks to determine if compounds are potentially harmful. Traditionally, this has been the focus of most of the Center's resources (most of the resources of toxicological research). This work, however, has been based on a number of assumptions that have not been adequately tested. NCTR is deemphasizing standard assays such as:

- The seven whole animal, two-year toxicity studies under FDA/NTP cooperative programs including Gentian Violet, Sulfamethazine, and selected antihistamines; and
- The conduct of unscheduled DNA synthesis and related short-term assays.

NCTR is redirecting its resources to emphasize activities such as:

- Programs to answer questions about animal testing associated with assumptions used when risk assessments are made;
- The development, modification and validation of in vivo biochemical, immunological and genetic methods to detect toxicity; and
- Continued investigation of neurochemical and postnatal behavioral endpoints as a function of prenatal exposure to neurotoxins.

Exposure Assessment.

Exposure assessment is the area which is the most limiting factor in risk assessment. The goal of work in this area is the development of measures of exposure at the molecular level which are comprehensive and obtainable in humans. This program includes:

Biochemical Toxicology.

- Development and validation of biomarkers of toxic exposure at the molecular level in order to differentiate between dose of toxicant in the environment and the biologically effective dose;
- Continuation of collaborative efforts with: a) the Veteran's Administration (for local access to human tissue and data); b) NIOSH (for national access to human tissue and data); and c) the Center for Environmental Health, CDC (for epidemiological data specifically on toxic chemical exposure) to apply the new methodologies of the biomarker program across species and as a function of subpopulations;

- Efforts to identify biochemical markers of tumor promotion as a function of tissue and species, and differential immunological susceptibility;
- Elucidation of the nature and role of specific biochemical detoxification pathways and their relationship to the use of biomarkers in testing the assumptions underlying exposure assessment; and
- Extension of our knowledge of the relationship of specific types of DNA damage to their biological effect to form the basis of quantifying effective exposure.

Reproductive and Developmental Toxicology.

- Extend the knowledge from the field of biochemical toxicology to the elucidation of the events occurring between maternal exposure to a toxic compound and fetal maldevelopment;
- Extend effort in the fields of pharmacokinetics and pharmacodynamics in order to understand the distribution of the chemical, the amount delivered to which organ site, the amount delivered to fetal tissue as well as maternal tissue and the time required for the chemical and its metabolites to achieve this distribution and dissipate; and
- Continued investigation of mechanisms in developmental toxicology in the context of modulation of toxicity, with emphasis on comparative metabolism between species in order to compare exposure between species.

Genetic Toxicology.

- Continued study of the relationship between total damage to the DNA, damage at specific sites, and persistence of the damage as it is related to the modulation of toxicity in order to better describe effective doses; and
- The study of organ, tissue and/or cellular specificity of certain chemicals, single-strand and double-strand DNA breaks, binding and specific adduct removal from DNA, and frequency of induced sister chromatid exchange in chromosome aberrations as these factors relate to modulation of toxicity.

Microbiological Toxicology.

- The continued exploration of the action of intestinal tract microflora on potentially toxic chemicals (e.g., gentian violet). In some cases those chemicals are activated to a carcinogenic state, in other cases they are converted into a less toxic state depending on the manner in which the microorganism breaks down (metabolizes) the chemical. In either case, what the body is exposed to is the result of not only what is ingested but also what is transported across the lumen after microflora and microfloral metabolites become involved in the process.

Hazard Assessment.

Hazard assessment is that aspect of risk assessment involved in determining the human response to a given level of exposure. To be successful, we must continue to become more knowledgeable about mechanisms of toxicity. Specifically we will:

- Continue the work of providing knowledge of specific genes affected by specific chemicals, and combine that with knowledge of whether humans metabolize chemicals to the same compound as test animals and whether humans have a different set of enzymes that either protect the gene from damage or promote that damage;
- Continue the program of determining modulators of toxicity. The first projects in this program relate to nutritional parameters which affect a number of toxicological endpoints;
- Synthesize the data on species differences be they concerned with metabolic pathways, genetic construction, or enzyme systems that change the toxicity of the same chemical between species; and
- Define the assumptions underlying these data which enable the mathematical and statistical definition and explanation of the potential for human harm associated with different levels and routes of exposure.

Risk Reduction.

Risk reduction is a part of risk management that takes advantage of the detailed knowledge of toxicity at the molecular level and the aspects of the methods that either contribute to or subtract from a chemical's toxicity to define ways in which the chemical would no longer pose the same high level of toxicity. Activities in this category include:

- A focusing of programs in biochemical toxicology on problems of risk assessment and risk reduction;
- Continue programs to understand the activation or inactivation of toxic agents by gut flora in the interest of altering this flora in appropriate situations. This program will also explore the effect of microflora found in soil on potentially toxic chemicals. In some cases with the goal of degrading chemicals (e.g., toxic waste dumps), but also the goal of determining the potential for activation that could affect the food supply;
- Continue and enhance cooperative programs with EPA relative to the thermal destruction of toxic compounds; and

- Continue programs in reproductive and developmental toxicology to provide opportunities for significant societal benefit through identification of the time during pregnancy that one is more susceptible to potential fetal harm and identification of the level of chemical exposure necessary to avoid that harm.

Program Interaction:

Other FDA Programs

- Provide assistance to research efforts of other FDA centers for over 30 research projects, including saccharin, sulfamethazine, gentian violet, various food additives, and antihistamines.
- Provide training for FDA investigators in computer technology, as it relates to good laboratory practices.

Other Federal Agencies

Environmental Protection Agency(EPA):

- Collaborate in the operation of a pilot incinerator at NCTR for completely destroying solid toxic wastes. This project is directed to resolution of problems of toxic waste dumps.
- Conduct consensus workshops concerning toxic substances of great economic importance.

National Toxicology Program; National Institute of Environmental Health Sciences (NTP; NIEHS):

The NTP was established within the Public Health Service in 1978 to coordinate research in toxicology and to strengthen the science base of toxicology. All interagency agreements concerning NTP are made with NIEHS. The NCTR contributes to this program to:

- Evaluate the toxicity of selected chemicals for NTP.
- Implement the Toxicology Data Management System in approximately 20 contract labs.

Department of the Army (DOA):

- Provide scientific support in information retrieval, exposure studies, pathology evaluations, chemical analyses, and short-term tests.
- Conduct studies on reproductive effects in laboratory animals after exposure to dilute concentrations of the compounds sarin and soman.
- Conduct range finding, 90-day, multi-generation, dominant lethal and delayed neuropathy tests on the compounds sarin and soman.

National Institute for Occupational Safety and Health; Centers for Disease Control (NIOSH/CDC):

- Develop a joint project to develop biological markers to detect human exposure to toxic agents.

National Institute for Drug Abuse (NIDA):

- Determine if chronic exposure to delta-9-THC (THC) or marijuana smoke produces permanent or long lasting behavioral impairments and/or neuropathological alterations.

National Institute on Aging (NIA):

- Develop colonies of aged rats and mice subjected to dietary restrictions to be employed for biomarkers of aging research.

Consumer Product Safety Commission (CPSC):

- Provide assistance in evaluating selected consumer products (acute studies, skin and eye irritation).
- Provide scientific support in information retrieval, exposure studies, chemical analysis of drugs, short-term testing, and pathology evaluation of animal tissue.
- Develop test methods and provide analytical data on levels of volatile nitrosamines in baby pacifiers to aid in regulation of affected products.

Responsible Contact:

Ronald W. Hart, Ph.D. - Director, National Center for Toxicological Research

September 1985

PROGRAM RESOURCE SUMMARY

National Center for Toxicological Research¹

Project Title
National Center for Toxicological Research TOTALS

FY 86 RESOURCES			
Totals		Percent of \$	
FTE	\$ (000)	Program	FDA
288	\$22,284	100%	5.4%
288	\$22,284	100%	5.4%

FIELD/HQ DISTRIBUTION OF 1986 RESOURCES				
FTE		\$ (000)		
FIELD	HQ	FIELD	HQ	
0	288	0	\$22,284	
0	288	\$ 0	\$22,284	

¹Resources reflect FDA FY 86 President's Budget.

National Center for
Toxicological Research